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General

HOST ENVIRONMENT INTERACTION IN PULMONARY CARCINOGENESIS
A Review of the Literature up to 1966

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Medical History
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PART TWO: LITERATURE PRIOR TO 1950

CHAPTER IV. THE 1940'S
POSTWAR PUBLICATIONS EXPLOSION ON CARCINOGENESIS

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CHAPTER IV. THE 1940'S.
POSTWAR PUBLICATIONS EXPLOSION ON PULMONARY CARCINOGENESIS

INTRODUCTION

After the atom bomb explosion in Japan, World War II ended. This became the beginning of a phenomenal increase in the list of suspected carcinogens that were categorized into the following: (a) radioactive compounds resulting from atom bomb explosions, uranium mining, and plutonium purification; (b) new industrial compounds consisting of heavy metals, synthetic organics and intermediates in the work environment and released into the ambient air, water and soil; (c) pesticides, food additives, pharmaceuticals and other household products that were not only useful but also caused health hazards to consumers; (d) vehicular and factory emissions, resulting from increase in availability of fossil fuel products; (e) consumer products, such as cigarettes, alcohol and non-alcoholic beverages. There was a "publications explosion" on the subject of carcinogenesis which was the outcome of a combination of increase in manpower, funding and research facilities devoted to cancer in general and of lung cancer in particular.

This review on the publications explosion occurring during the 1940's is being undertaken at a time when a new Clean Air Act is being considered by the United States Congress. Although scientific and medical publications leading to the 1970 Clean Air Act, 1977 Amendments and 1989 Proposal are discussed in Part

Four, Chapter VII, it is important to recognize that ambient air pollutants were suspected pulmonary carcinogens prior to the 1940's. The present National Toxicology Program list of suspected carcinogens includes specific constituents belonging to the above list such as (a) polonium; (b) arsenic; (c) formaldehyde; (d) benzopyrene; and (e) asbestos. Coincidentally, each example was present in cigarette smoke during the 1940's, and data on tobacco smoke constituency were used to support the concept that cigarette smoking caused lung cancer.

Harris' State of the Art Report

Like preceding Chapters, the lung cancer literature selected by Harris in his SOA expert report is compared with the literature he did not use. Each Topic (A to E) is introduced by highlighting Harris' opinion. The last Topic (F), contains a critique of Harris' summary statements based on publications prior to 1950. There are corresponding counter-statements adjacent to each of Harris' SOA statements.

Since the over-riding purpose of this review is to discuss host-environment interactions in pulmonary carcinogenesis, Harris' opinion is not my only concern. Quotations from articles published prior to 1950 have been selected as a background to review of the literature from 1950 to 1966 (Part Three). This review is not limited to the suspected role of cigarette smoking only, as Harris did in his SOA report, but is extended to include

other suspected occupational/environmental causes and host susceptibility to lung cancer.

Hueper's Monographs, Reviews and Other Publications

I selected the late Wilhelm C. Hueper as a posthumous expert because from 1928 to 1972, he published statements questioning any causal importance of cigarette smoking in patients with lung cancer (see pages 23, 64, 162). The monographs and reviews by Hueper during the 1940's were as follows:

Monograph (a): *Occupational Tumors and Allied Diseases* **(4207)**. This is the first comprehensive monograph by an American author devoted to tumors of workers. This is one of a dozen **highlight publication** among over 600 in this Chapter. Bibliography number in **bold face** represents my selection of highlight publications for the 1940's.

Monograph (b): *Environmental and Occupational Cancer* (4804) was published under the auspices of the Cancer Control Branch, National Cancer Institute. The preface had no signature and was probably written by Hueper's superiors listed in the front page: C. St. J. Perrot, Chief of Division of Public Health Methods; Leonard A. Scheele, Surgeon General; and Oscar R. Ewing, Federal Security Agency Administrator:

> "This study presents a comprehensive review of current knowledge of the environmental causes of human cancer. **Dr. W. C. Hueper, whose major interests have been in the fields of environmental and occupational carcinogenesis,** has collected and analyzed the most important known facts on this problem, both domestic and

from abroad. His summation of the data and his evaluation of the significance, reported in compact and usable form, should be of very real value to everyone concerned with the Nation's health.

The conclusion is inescapable that exogenous agents, particularly of industrial origin, are important factors in the causation of certain types of cancer. It is true that neoplasms of known environmental etiology comprise only a part of the total cancer incidence in the United States. However, the fact that there seems to be a constant though gradual increase in the appearance of these cancers in the general population is swiftly making occupational carcinogenesis a public health problem of very real importance. Epidemiologically, for example, much more needs to be done to reveal additional substances guilty of carcinogenic activities.

It is a problem which admits of no simple solution, as Dr. Hueper makes clear. No one agency, governmental or private, can solve it. Only a carefully coordinated and integrated program of technical and social controls, supported by the cooperative efforts of government, private health organizations, the medical profession, management and labor, can begin to cope successfully with the growing occupational hazard. Such a program deserves the most careful consideration and awareness of everyone concerned with the health of the American people." page iii, (4804)

The role of governmental agency in promoting cancer research is discussed below (Topic A).

Hueper's other publications. The remaining publications during the 1940's were on the following subjects: epidemiology and prevention of occupational cancer (4340) (4637) (4943) (4944); experimental carcinogens (4147) (4239) (4535) (4536); and experimental atherosclerosis (4208) (4238) (4444) (4534) (4537). Tobacco smoking was not discussed by Hueper in his publications although some constituents of tobacco smoke and tobacco additives were mentioned because of their occurrence in coal tar products.

Lung Cancer Monographs in English

Almost all monographs and review articles on lung cancer were written by Americans. British authors are noted in the following list, arranged according to year of publication:

Monograph (c) Reinhoff: *Surgical Treatment of Malignant Tumors of the Lung* - In: Treatment of Cancer and Allied Diseases, G. T. Pack and E. M. Livingston, editors (4003). Reinhoff was a thoracic surgeon from Johns Hopkins Hospital. Like most of his articles on lung cancer published in the 1930's, this chapter contained surgical procedures with no discussion of etiology.

Monograph (d) Holmes & Ruggles: *Roentgen Interpretation* (4101). A chapter was devoted to "Lung Fields," with special reference to differential diagnosis of lung cancer. There was no discussion on etiology of lung cancer.

Monograph (e) Reimann: *New Growths in the Lungs* (4204) (4303) - In: Textbook of Medicine by American Authors, R. L. Cecil, editor. Reimann was a Professor of Medicine at Jefferson Medical College Hospital at Philadelphia and had written original articles on lung diseases. The paragraph on the etiology was brief:

> "The etiology, of course, is unknown but all factors are said to have one quality in common, namely chronic irritation. The irritation may be caused by chemical, mechanical, bacterial, radioactive and perhaps thermal means. Some believe that chronic irritation plays no role." page 958, (4204)

Monograph (f) Christian: *Tumors of the Lungs and Bronchi* - In: Principles and Practice of Medicine, Semi-centennial edition

by Osler (4205). The following paragraph was on etiology:

> "There is no clear explanation of the increase in these tumors or of reasons for it, if the increase is actual. Irritation of the bronchial mucous membrane by gases or tar is suggested. In the workers in the Schneeberg and Joachimstal mines there is a high incidence, perhaps due to radioactive material in these mines. As to age it is well to recognize that it may occur in young adults." page 852, (4205)

The remainder of the three-paged chapter were titled Pathology, Pathological Physiology, Symptoms, Physical Signs, Diagnoses and Treatment.

Monograph (g) Hadfield & Garrod: *Recent Advances in Pathology* (4209). The authors were from St. Bartholomew's Hospital in London and had three pages of text devoted to etiology of lung cancer:

> "Such suggestions as have been made to account for the genesis of lung cancer, and more particularly for its supposedly increasing frequency, are almost wholly unsupported by evidence. x x x With the increasing tendency to regard cancer as the product of long-continued irritation, it is inevitable that attention should be directed to inhaled irritants. Gassing during the war and its sequelae apparently do not predispose to cancer, nor is there any good reason for incriminating tobacco smoke. There is no statistical evidence to indicate that exhaust gases from petrol engines are carcinogenic, but a study of occupational distribution extensive and detailed enough to yield significant data bearing on this point has yet to be made." pages 222-223, (4209)

Other paragraphs relating to occupation exposure and host disposing factors are quoted below (Topics D and E). It suffices to mention here that experimental studies on road tar are quoted but not those on tobacco tar experiments conducted prior to 1942.

Monograph (h) Stern & Willheim: *The Biochemistry of Malignant Tumors* (4301). The spread of Nazism led to the emigration and separation of the authors, with publication of the article by one of them, and an unknown ending as to whether the writer was reunited with his collaborator (see page 24). This monograph was the first one devoted to the biochemical features of cancer, specifically, influence of chemical carcinogens and cancer reaction of biologic tissues.

Monograph (i) Henry: *Cancer of the Scrotum in Relation to Occupation* (4601). The author was employed by H. M. Medical Inspector of Factories, the British office that antedated by 50 years the American Occupational Safety Health Administration (OSHA). Pertinent portions are discussed below under Topic D.

Monograph (j) Henry: *Occupational Cutaneous Cancer Attributable to Certain Chemical Industries* (4748). The author wrote this review after he joined the research staff at the Royal Cancer Hospital (Free) of London. This monograph has been widely quoted to support carcinogenicity of "tobacco tar" by drawing similarities in chemical constituents of tobacco smoke condensate and coal tar (see Topic D).

Monograph (k) Willis: *Pathology of Tumors* (4802), a highlight publication. This book was written while the author was Professor of Human and Comparative Pathology at the Royal College of Surgeons. He was formerly from the University of Melbourne in Australia (4176). Willis had not published original

studies on lung cancer, but his monograph was accepted as an authoritative source of reference, probably because Ewing's monograph was not revised after he died in 1943. The bold face sentences are key quotations. Preceding and following sentences are included to place the essential quotation in proper prospective.

> "Every known inhaled substance and almost every known infection of the lungs has, by one writer or another, been claimed or suggested as a possible factor in the causation of pulmonary carcinoma. The subject is then confused and confusing; and there is good reason for a succinct statement separating definitely established facts from a mass of speculation - even at the risk of seeming a little over-dogmatic. **The whole subject has been well reviewed by Hueper.**
>
> There is no satisfactory evidence that any of the common infections of the bronchi or lungs predisposes to carcinoma. Silicosis is of doubtful causative importance, and the evidence regarding the other forms of pneumoconiosis also is inconclusive. It is quite possible that the inhalation of carcinogenic hydrocarbons or other substances in soots, smokes and dusts, **including tobacco smoke, is an important causative factor, but proof of this will entail much more pathological and experimental research.** There are strong grounds for believing that inhaled radio-active substances can cause lung cancer, but experimental verification of this has yet to be made. Further study is required also on the possible carcinogenic properties of inhaled arsenic, chromates and nickel compounds. Neither trauma nor heredity plays any significant part in human lung cancer." pages 362, 365-366, (4802)

Monograph (1) Fried: *Bronchogenic Carcinoma and Adenoma* (4801); **a highlight publication.** This is a revision of an earlier monograph (3201) and review (3101) by an internist at the Montefiore Hospital for Chronic Diseases, New York (see Chapter III, page 161). The section on tobacco etiology included the following:

"It is commonly accepted that in order to produce an infectious disease in an animal, the virulence of the germ, the 'dose' of infectious material as well as the susceptibility of the host should be taken into account. Moreover, the susceptibility of an animal to a given species of bacterium not infrequently depends upon the route by which the organism is introduced.

The experimental pathologist has only lately begun to realize that the **application of some 'irritant' is not alone sufficient always to produce malignant disease,** that not every 'irritating' substance will lead to a malignant disease and that even 'verified' cancerogenous agents will not infrequently fail to excite a particular structure to participate in the development of a malignant process.

Fibiger, for instance, has demonstrated that rats fed with the *Spiroptera neoplastice (Gongylonema neoplasticum)* will acquire cancer of the stomach, while other spirochetes will cause no malignant disease. Similarly, coal tar products will induce a cutaneous but not a rectal cancer in mice. Again the *Spiroptera neoplastica* leads to an epithelial malignant disease while the *Cysticercus fasciolaris*, the larva of the cat tapeworm *Taenia crassicolis*, induces as a rule, a malignant connective tissue tumor of the liver. Likewise in grafting malignant tumors it was observed that whereas the inoculations into the brain, the anterior chamber of the eye, or the muscles will lead in most instances to a vigorous growth of the transplanted neoplasm; subcutaneous, intravenous and the intraperitoneal grafts will 'take' from 20 to 25 per cent only. The intracutaneous method will yield still less favorable results. Apparently the immunobiologic principles which have been involved in the study of infectious diseases deserve to be considered in the study of experimental and spontaneous tumors. **The carcinogenic substance, the host and the particular organ or structure attacked should be considered.**

Recently a few investigators made the suggestion that smoking of tobacco is in all likelihood a causative factor. The fact that bronchiogenic cancer is prevalent in the male was considered to favor this theory. Nicotine, pyridine, phenolic bodies, constituents of tobacco, were looked upon as 'irritating carcinogenic substances.' **However, these chemicals have never been proven carcinogenic.**

Studies of lungs of heavy smokers failed to reveal changes in bronchi or pulmonary parenchyma that could be attributed to smoking. Since tar is the only carcinogenic substance which the smoking of tobacco yields,

> attempts were made to observe its effect on laboratory animals. Tobacco tar has, therefore, been applied to the skin and mucosa of mice but no cancers were obtained. Flory, by destructive distillation of tobacco, developed papillomas but no carcinomas. In another series of experiments rabbits were painted with tar obtained by smoking tobacco in pipes. Here, too, no carcinomas were produced. **Evidence thus far adduced is contrary to the idea that bronchiogenic cancer is caused by tobacco."** pages 66-68, (4801)

The above boldfaced quotations are important in showing that up to the late 1940's, evidence that tobacco as a lung carcinogen was not acceptable to Fried. That Fried altered his opinion in the next revision of the monograph will be reviewed in Chapter V, the 1950's.

A review of the monographs published during the 1940's revealed that cigarette smoking was not in the post World War II list of carcinogens. Authorities on lung cancer questioned the validity of evidence in support of cigarette smoking as a cause of cancer. On the other hand, evidences that occupational and environmental factors caused lung cancer were accepted by several authorities. Details are further discussed in the remainder of this chapter.

A. INCREASING INCIDENCE OF CANCER

The cancer literature during the 1940's included a discussion of whether in a given community, the incidence of cancer as a whole has increased demonstrably since the turn of the century. Willis, in his 1948 monograph on *Pathology of Tumours* made the following conclusion:

> "There is no evidence that the real incidence of cancer as a whole is changing, save in so far as the age-compositions of populations change, or as people are prevented from dying of other diseases. Hoffman and others who have believed that there has been a real and alarming increase of cancer in all civilized countries, have underrated the great degree of fallibility in the registered causes of death and the degree of improvement effected in these by improved methods of diagnosis." page 86, (4802)

The above paragraph is contained in Willis' chapter entitled "The Statistical Study of Tumours" that also included a discussion on degree of accuracy of diagnosis:

> "Carcinoma of the lung had been correctly diagnosed in only 61 per cent of cases; and the proportion of false positive to correct diagnoses (D + E:A) was 1 to 5. If no necropsies had been performed, the number of death certificates which would have borne the diagnosis 'carcinoma of the lung' would have been not more than 52 (A + D + E), i.e. 73 per cent of the actual number; indeed the number would have been fewer than this, because in several cases the clinician, relying mainly on radiographic reports, would have committed himself to no more specific diagnosis than 'pulmonary neoplasm' or even only 'intra-thoracic neoplasm'. All of the 15 misdiagnoses of group C had been due to clinically obtrusive secondary growths. These were in the brain in 4 cases and the clinical diagnoses had been 'cerebral tumour'; in a fifth case (of group B) cerebral metastases had led to a clinical diagnosis of 'confusional psychosis'." page 74, (4802)

Hoffman, in the first quoted paragraph, was the same researcher selected by Harris in his report [SOA 5.1, SOA 5.2, SOA 5.3, SOA 5.7]. Hoffman wrote a 1915 monograph entitled *The Mortality from Cancer Throughout the World, Newark, New York*. I was able to obtain a copy of a later monograph (3701), but not of the earlier one.

Cancer Mortality

The debate on whether there was a real increase in incidence of cancer was based on interpretation of results of death records from hospitals contrasted with those reported by governmental offices for vital statistics. Hospital records that question any real increase in incidence are discussed below.

University of Texas Medical Branch at Galveston. Rigdon and Kidder (4960) reviewed the frequency of cancer in 7500 routine autopsies conducted between 1941 and 1948. Although there was an increase in cancer progressively since 1905, there was a corresponding decrease in tuberculosis.

> "There has been an increase in the number of autopsied cases of cancer during the past forty-three years. This increase may have resulted from the fact that death from infectious diseases has decreased and, today, a person is more likely to die from cancer than forty years ago. **These data do not support the opinion sometimes expressed that cancer is actually on the increase.** From a study of the records in the Department of Pathology on postmortem examinations between 1905 and 1948 and the death tables in the Vital Statistics of Texas, it would appear that actually more persons die from cancer and associated diseases than is indicated by data compiled from routine death certificates." pages 247-248, (4960)

Johns Hopkins Hospital at Baltimore. From 1927 to 1938, Pearl and Bacon conducted biometrical studies on necropsies. Approximately 12.2 per cent of necropsies showed some form of malignant tumor, and that in the necropsied population, malignant tumors of all sorts occurred from two to three times more frequently among white persons than they do among colored persons (2733). In males, malignant tumors occurred most often in the alimentary tract and its associated glandular organs, and in females, in the reproductive system (2841). Based on Family History Records of the Department of Biology, Pearl examined longevity. The death rates of 6813 men, unselected except as to their tobacco usage, suggested the following interpretation:

> "In this sizable material the smoking of tobacco was statistically associated with an impairment of life duration, and the amount or degree of this impairment increased as the habitual amount of smoking increased. Here, just as is usually the case in our experience in studies of this sort, the differences between the usage groups in specific mortality rates, as indicated by q_x, practically disappear from about age 70 on. This is presumably an expression of the residual effect of the heavily selective character of the mortality in the earlier years in the groups damaged by the agent (in this case tobacco). On this view those individuals in the damaged groups who survive to 70 or thereabouts are such tough and resistant specimens that thereafter tobacco does them no further measurable harm as a group." page 217, (3876)

That tobacco smoking may account for reduced longevity was not the only explanation offered by Pearl. He recognized that individuals were also habituated to tea, coffee, alcohol, opium and betel nut, and that over 90 per cent of all adult human beings habitually make use of one or more of the substances.

Pearl also discussed heavy physical effort and hereditary influences on constitutional features of individuals (3877, 3878, 3881).

Metropolitan Life Insurance Records of Physicians. Dublin and Spiegelman have analyzed the longevity and mortality of physicians and specialists. Physicians under 45 years have a much lower death rate than the general population of the same ages, reflecting their select physical condition and better socio-economic status. Later in life, physicians have the higher death rate, and mortality from cardiovascular disease was considerably greater than in the general population. Cancer incidence was lower in physicians demonstrating the advantage of early recognition (4732).

The mortality rate of specialists as a group was only 70 percent of that of non-specialists. The rate of mortality from cancer among general surgeons was well below the record of any other specialty and also for non-specialists. Their advantage, interpreted by Dublin and Spiegelman, was a consequence of their training in early recognition of the condition and their knowledge of benefit of early treatment. On the other hand, roentgenologists, radiologists and dermatologists had a high rate of mortality from cancer and leukemia, suggesting strongly the effect of their exposure to dangerous radiations (4826).

The longevity and mortality of American physicians were important for comparing with British prospective studies reported

during the 1950's. Dublin and Spiegelman did not discuss smoking habits but in their oral presentation held at the 1947 Annual Session of the AMA, Helen Emerson of New York made the following comments:

> "While my studies of 1926, though less complete than Dr. Dublin's of today, showed essentially the same characteristic, may I be permitted to doubt the assumption offered this morning to the effect that 'knowledge of the causes of death of physicians may well point the way to effective preventive measures.' Not unless we have some rational inkling of the predisposing and precipitating etiology and find them to be preventable. The main cause, I believe, of this high rate among certain causes of death is that we are entirely, as a profession, whether a public health profession or a medical profession, wholly ignorant of the determining and predisposing factors that lead to these deaths from the cardiovascular-renal complex. We really know nothing useful as to the causative or preventive factors that lead to cardiovascular deaths in physicians or others in the decades above 60 years. Work, anxiety, sustained mental alertness, irregularity of rest, food and exercise are common to many others than physicians. x x x I see no reason to believe that the high rates for these conditions among physicians means anything more than that physicians have on the whole, been spared more commonly to live into the decades when nature takes their fate in hand and cuts the thread of life. There is little evidence that physicians as a class observe the precaution of periodic health examination, endorsed by the AMA as long ago as 1922, **nor is there any evidence of superiority of general hygienic practices by physicians, especially in matters of diet and habitual use of alcohol, and tobacco particularly.** I should say that we have not proved any point of superiority of physicians in the manner of their living, although there is probably for the medical student a more thoughtful regard for his health through the use of repeated chest x-ray examinations, particularly than for other persons likely to be separately recorded. I think we must learn more of functional pathology and the problems of metabolism, the natural history of aging, rather than to rely on comparison between physicians and the general public as evidence or explanation of differential death rates of physicians." page 1215, (4733)

Dublin responded to the above comments as follows:

> "Dr. Emerson would suggest that we really know next to nothing with regard to the preventability of the cardiovascular conditions. That doesn't seem to fit at all into what we, as public health people, are insisting in all our public statements. What is the basis of the entire campaign in the heart field and in the field of personal hygiene? Does the physician help himself? Does he follow what he knows and what he tells his patients? Dr. Emerson himself later indicated that there was a good deal of merit in the criticism that the doctor himself doesn't follow his own mandate with regard to diet, with regard to rest and with regard to exercise. The point that he made with regard to the high mortality from cardiovascular disease in those communities which have the lowest death rates and the highest sanitary standards has no bearing here. I know perfectly well that lives are saved from typhoid, tuberculosis and diphtheria, so that an increasing proportion of deaths will occur at the higher ages. By the end of the century 90 per cent of all deaths will be beyond age 45." page 1215, (4733)

The above dialogue was representative of how epidemiologist publicly argued on interpretation of mortality statistics. Dublin's prediction on mortality by end of the century appears to be doubtful based on 1988 figures.

Cancer mortality in Sweden. Hammerstrom analyzed death statistics for seventy years. The mortality for cancer in 1938 was 152 deaths/100000 inhabitants. His conclusions were as follows:

> "This study aims to contribute to the discussion whether there is an actual increase in the cancer frequency. The author maintains, that the solution of this problem lies mainly in mortality statistics. Several phases of cancer statistics are discussed in a review of the literature. The importance of age grouping of the materials is emphasized. Statistics of cancer mortality from districts with well analyzed causes of death supports the assumption, that no actually increase in the cancer frequency exists.

> The authors own investigation is an inquiry into the cancer mortality in Stockholm during the last seventy years. It is shown that the official statistics of this city is a valuable source for the study of cancer frequency. **The present study of the figures of Stockholm supports the opinion, that there is no actual increase in cancer frequency.** Finally the author gives figures to illustrate the cancer mortality throughout Sweden. The results of this review agrees with the previous conclusion." page 583, (4231)

The above conclusion applied only to Sweden since other European countries and the United States varied as much as 20 per cent in cancer mortality rates.

Cancer morbidity. Cancer morbidity records were derived from individual clinics and hospitals that were of limited value in actually counting individuals known to have cancer. Cancer registries were organized in the following states:

	Per 100,000
Connecticut (4546) (4547) (4823) (4833) (4853) (4854)	207.8 cases
Delaware (4886)	Not expressed
District of Columbia (4539)	131.3 deaths
Kansas (4511)	127.0 deaths
New Jersey (4977)	No figures reported
Massachusetts (4243) (4454)	1.1% annual increase
New York (4648) (4649)	increase in 5-year survival

The results were not expressed uniformly because of differences in scope and financial support from state to state. The results from federal agencies were more extensive in part due to higher level of financial support and larger personnel.

United States Public Health Service. Dorn, a senior economist, conducted a survey of hospitals, clinics and private physicians in ten selected areas listed below. The population of these was numbered slightly more than 13 million in 1940 or about

10 per cent of total, and 18 percent of urban population in the United States. His conclusions were as follows:

> "In 1940 there were 158,335 deaths attributed to cancer registered in the United States. The number of living cases is unknown. However, an estimate of the number of persons receiving treatment for a malignant tumor can be obtained by multiplying the population of the United States reported by the census of population in 1940 by the illness rates found in this study.
>
> Although these data were collected from physicians and hospitals in metropolitan areas, it is believed that they may be used without serious error to estimate the number of cases of cancer in the entire country. Mortality reports indicate that the death rate from cancer is higher among urban than among rural residents. Part of this difference may be due to more accurate diagnosis of the cause of death in urban areas so that the real difference in the death rates is probably less than the observed difference. Furthermore, the illness rates reported here are almost certainly less than the true but unknown rates. Some persons who die from cancer have never received any treatment for the disease. When all factors are taken into consideration, the illness rates reported here undoubtedly understate rather than overstate the number of persons with cancer in the population.
>
> On the basis of the prevalence rates found in this study, it is estimated that there are about 475,000 to 500,000 persons under treatment of cancer at any given time in the United States. About 300,000 new cases of cancer are diagnosed for the first time during each year. In addition to these cases are those who have been treated and cured as well as those with an undiagnosed tumor. The number in the latter two categories is unknown." pages 112-114, (4432)

The above conclusions of Dorn represented the first cancer morbidity estimate for the entire United States, derived by pooling illness rates in ten areas, namely: Atlanta, Pittsburgh, Detroit, Chicago, New Orleans, Dallas and Fort Worth, San Francisco and Alameda County, Birmingham, Philadelphia , and Denver. The cancer death rates for 1943 were listed by another

investigator (4539) for three of the selected areas: Detroit 102.3, New Orleans 155.5, Philadelphia 188.9/100,000. Note that there was a difference of 87 deaths/100,000 inhabitants between Detroit and Philadelphia and may even be more if rural areas were considered (4457). I have not had time to complete a comparison but the general criticism of Dorn's study is as follows: the pooling of all cancer illness from ten areas overlooks differences in occupational/environmental factors and host susceptibility.

United States Naval Service. The cancer incidence rates among naval personnel were derived from autopsy records of naval hospitals at Brooklyn and Philadelphia. The absolute number of cancer cases was increased but the proportion relative to all autopsies remained essentially unchanged during the 1940's (4614) (4623) (4965). The mortality rate from skin and lip cancer in the Navy was about 3 times higher than in the average population of the same age composition. Peller and Stephenson attributed the increase to the peculiar conditions of life in the Navy, i.e. the prolonged exposure to the sun's rays, to open air and to salt water (3786). Coincidentally, there was a greatly diminished morbidity and mortality from all other cancers. They suggested that by exposing young men to strong skin irritations, there was a reduction in susceptibility to cancer of internal organs. This theory was not applied to interpretation of skin painting experiments in animals.

United States Veteran's Hospital. Schrek and Allaben reviewed the 2407 admissions to the tumor clinic (Hines, Illinois). A relatively high percentage (51%) of patients with carcinoma of exposed skin came from the Southern States, but low percentages (17% and 12%) with cancer of the stomach and testis were also from the South. Patients with carcinoma of the unexposed skin and lip were relatively rare (4567).

Cancer Institutes and Organizations

As infectious diseases were being controlled by public health measures, cancer was increasing in importance. The National Cancer Institute Act of 1937 set in motion a federal commitment to cancer control although this was preceded by formation of cancer control programs at state level. Voluntary organizations started in large cities, followed by statewide groups, then a national organization, and finally, international research conferences.

National Cancer Institute. The 1937 Act created the Institute, which was charged with the authority to "provide training ... provide fellowships .... procure and lend radium ... cooperate with state agencies in prevention, control and eradication of cancer." The objections of the American Medical Association to promulgation of the Act, difficulties in selection of National Advisory Cancer Council, and level of funding were reviewed in *History of Cancer Control Program*

(7701). A contemporary description the National Cancer Institute Program was prepared by Carrigan and Marshino (4821). The summary needs to be quoted in detail because in subsequent decades, funding for the Institute increased in levels that were not predicted by those who sponsored for, and those who lobbied against the 1937 National Cancer Institute Act:

> "The program of the National Cancer Institute is directed at two complementary objectives: (1) to try to find the ultimate solution of the cancer problem through research designed to give us a better understanding of the causes of cancer and more effective methods of diagnosis and treatment; and (2) to save as many lives as possible through the use of our present methods of diagnosis and treatment of cancer.
>
> To attain the first objective, the Institute is conducting in its own laboratories numerous studies in the fields of biology, biochemistry, chemotherapy, endocrinology, biophysics, pathology, and biostatistics. Clinical studies are conducted in the cancer clinic of the United States Marine Hospital, Baltimore, Md., and in two other cooperating hospitals. A greatly expanded clinical research program is envisioned in the plans for a research hospital on the grounds of the National Institute of Health. A research grants program supports cancer research in many different fields of investigation in a large number of laboratories throughout the United States, and in two foreign countries. These grants make it possible to bring into the cancer program already existing laboratories and some of the ablest investigators in various fields of science involved in the study of cancer. Grants to help expand and equip outside laboratories will be made in order to provide more research facilities. Research fellowships are granted to provide larger numbers of trained scientists to staff cancer laboratories.
>
> To attain the second objective, the Institute is carrying on a cancer control program. This program includes grants to State health agencies and other agencies and institutions to enable them to undertake or to expand cancer control programs, including the provision of more adequate cancer facilities and services for the cancer patient and studies to gain new knowledge applicable to cancer control problems; grants to medical and dental schools to provide more adequate

> training in cancer for medical and dental students; a clinical traineeship program to provide training in cancer diagnosis and treatment for physicians who wish to specialize in this field; loans of radium to hospitals; special studies and demonstrations; educational activities; consultant and advisory services; loans of personnel; and stimulation of cancer control activities by other agencies.
>
> This over-all program represents the combined planning of the National Cancer Institute and the National Advisory Cancer Council. It has been designed to attack the cancer problem on all fronts and represents the best that can be evolved on the basis of our present knowledge and experience. The effectiveness of the program will be evaluated from time to time and changes made to conform to the new knowledge gained by the various activities." pages 516-517, 4821)

The U.S. Public Health Service conducted surveys on biologic factors such as marriage trends in selected counties (4030), cancer morbidity rates in selected cities (see above, page 436), and occupational disease surveys (see Topic D).

Cancer philantrophic organizations. Spencer, who was the chief of the National Cancer Institute in the early 1940's, reviewed the role of philanthropic foundations that exclusively used their funds for cancer research: Anna Fuller Fund, Finney-Howell Research Foundation, Inc., International Cancer Research Foundation, and Jane Coffin Childs Memorial Fund for Medical Research (4573). I have not found any information as to type of research supported by these foundations. The Donner Foundation (formerly the International Cancer Research Foundation) sponsored the publication of an *Index to Literature of Experimental Cancer Research, 1900 to 1935* (4803). This was a source of reference for Harris in preparing his ERR. Approximately half of referen-

ces on tobacco tar listed in the Index were used by Harris in his SOA report. Titles on coal tar were hardly mentioned by Harris, whereas half of them are discussed below (see Topic D).

American Cancer Society. There were three publications that recounted the history of this voluntary organization. Triolo and Shimkin, from Fels Research Institute in Philadelphia, reviewed the origins and organization during the first four decades (6911). Patterson wrote about the *Alliance Against Cancer,* including the conflict between physicians and businessmen in controlling the American Cancer Society and its predecessor, the American Society for Control of Cancer (8703). Breslow, wrote *A History of Cancer Control in the United States* (7701). In the private, non-governmental sector, organized cancer control programs have been dominated by the American Cancer Society.

> "Over the years, the American Cancer Society has evolved an ambitious, vital program that goes to the heart of cancer control: public and professional education, patient services, intramural and extramural research and fellowships. Its continued success in capturing some of the unexpended capital of Americans year after year has provided half a billion dollars of donated monies and at least an equal amount of in-kind contributed public services over the past 64 years.
>
> The Society is regarded, quite correctly, as possibly the most powerful and pervasive voluntary health agency in the world. There is scarcely a hamlet in the nation where the familiar sword and caduceus symbol is not known. That trademark is particularly prominent each April, which was designated Cancer Control Month by presidential proclamation in 1938, the time each year when the Society's annual fundraising "Cancer Crusade" takes place.
>
> The American Cancer Society - and its antecedent American Society for the Control of Cancer - has set the tone of cancer control first in the voluntary sector and then, by direct influence, in the governmental sector.

> While today one might quarrel with the Society's cautious activism, or conservatism, the Society cannot be faulted for its forthright accomplishment in making the American public aware of cancer and aware that by prevention and early detection, the toll from this dread disease can be reduced. The Society has been the major producer of educational materials enhancing public understanding of the disease and its management. The Society has also been a major force in securing vast federal appropriations for cancer research, and, to a lesser extent, federal cancer control activities. The Society has been a formidable magnet: in its 64-year history, it has drawn upon the active participation of elected officials, professional and business scions, athletes, columnists and entertainers, not to mention thousands of health professionals and scientists.
>
> More than one percent of the nation's population - over 2.5 million Americans - are current ACS volunteers. About 300,000 are discernibly active, engaged in committee assignments and service activities; the balance are enlisted, often year after year, for the short-term spring exercise of raising campaign funds and broadcasting ACS educational materials.
>
> How did the American Cancer Society come to dominate the voluntary cancer control field - and the voluntary health agency movement itself? The answers lie in its origins, its continuity of volunteer leadership and management, its appeal to selected powerbrokers, and perhaps in the product itself - elusive as cancer is - which may insure that the American Cancer Society will remain in business for a long time." pages 775-776, (7701)

The above version of American Cancer Society activities is different from the description by Patterson entitled *The Dread Disease, Cancer and Modern American Culture* (8703). This book was written with the assistance of archivists and medical librarians, and appeared a year after Harris wrote his SOA report.

The American Society for the Control of Cancer was the antecedent organization of the American Cancer Society. During its existence (1913 to 1945), Clarence C. Cook was active and was

the Managing Director and Editor of its *National Bulletin*. This monthly publication contained financial reports (3338) (3767) (3870) (3966). It is not possible to comment on funding of research because there was no comparable voluntary health group during the 1930's and 1940's. Little wrote editorials on cancer research (4347), diet and cancer incidence (4154), and sections on Research and Education in *Cancer, A Study for Laymen* (4401). Although there were chapters devoted to common forms of cancer (skin, breast, uterus, stomach, rectum, bladder and prostate, thyroid), there was none devoted to lung cancer. The American Association for Cancer Research (6111) remained as the purely scientific organization that initiated National Cancer Conferences (4348) and International Cancer Congress, sponsored by the International Union Against Cancer (3988) (4890). The latter was assisted by the British Empire Cancer Campaign and other similar organizations in Europe (4413).

B. CASE REPORTS ON LUNG CANCER

In earlier chapters, the literature review on lung cancer consisted mostly of case reports, some epidemiologic studies, and a few animal experiments. The practice continued during the 1940's. In addition, there were publications that summarized clinical and necropsy data derived from scores of case reports from a hospital or clinic. The literature collected for this section is exclusively devoted to answering the question: What is the role of cigarette smoking, occupational/environmental factors and host susceptibility in lung cancer patients? There was hardly a clinical article entitled etiology. The search was conducted by random selection of articles on clinical diagnosis, surgical management and histopathological studies on lung cancer, with special attention to authors from cancer research centers and teaching hospitals. In the table below, there are over 236 lung cancer articles representing one-third of total clinical literature for the 1940's. About half of collected articles did not discuss etiology but nevertheless are included below because they are essential for a clinical expert to recall the diagnosis and management of llung cancer patients.

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Tabulated Case Reports

The headings are the same as those used in earlier Tables (Chapter Two, pages 74-77, and Chapter Three, pages 180-188), including investigator's names, geographical location, gender of patients, occupational and environmental factors, and hostal factors influencing predisposition or susceptibility to lung cancer. Out of 236 tabulated articles, only nine publications specified smoking habit of reported case reports, which is 4 percent of the clinical reports (4146) (4173) (4253) (4336) (4364) (4533) (4718) (4754) (4969). There were three additional articles that cited references on suspected role of cigarette smoke, yet failed to report the smoking habit of patients (4046) (4718) (4866). The available literature did not support Harris' SOA 5.13 statement that by late 1930's, it was a common practice to question smoking habit in suspected lung cancer patients. The total patients reported in the following table are as follows: 5908 males, 883 females, 4565 gender not mentioned, a total of 11356 patients with male to female incidence ratio of 6.7:1.

The column on hostal predisposition include racial background and occupational history. Outdoor workers are separated from those working indoors becauuse articles prior to 1940 suggested the causal role of fossil fuel products and fuel combustion emissions.

PRIMARY LUNG CANCER CASE REPORTS

State/Country (Ref)/Authors	Number/ Gender	Occupational Factors	Host Predisposition Clinical Data
Alabama			
(4249) Newhauser	1M	electric furnace operator	clinicopathological
(4765) Levy	1M		cardiac metastases
California			
(4081) Samson & Holman	4M 2F		surgery
(4087) Singer	2M		surgery
(4178) Goldman & Stephens	7M 1F		bronchial adenoma
(4229) Goldman	4M		surgery
(4263) Stephens	101M		classification
(4524) Farber & Edwards	45M 5F	9 laborers, 2 cooks 3 packers, 2 housekeepers	
(4580) Wood & Pierson	1F	telephone operator	alveolar adenomatosis
(4758) Jones	196 gender?		37% operable
(4771) Oechsli & Olson	2M		differential diagnosis TB
(4828) Farber et al	3M		sputum cytology
(4841) Jones		Review: early diagnosis	
(4877) Reitz	24M	navy veterans	
(4882) Shoemaker	1M		alveolar adenomatosis
(4887) Stein		Review: apical cancer	
(4888) Stein	131M; 33F		30% familial history
(4931) Farber et al	100 gender?	Review: cytology	
Colorado			
(4248) Newbuerger & Geever		Review: alveolar cell tumor	
Connecticut			
(4043) Hall	5M		apical tumor
(4079) Rosahn	86 gender?		diagnostic errors
(4056) Lindskog		Review: diagnostic errors	
(4644) Lindskog	82M; 18F		surgical exploration
(4849) Lindskog & Bloomer	100 gender?		surgical exploration
District of Columbia			
(4072) Perry	2M; 1F		question statistics
(4319) Amberson		Review: clinical features	
(4751) Hollingworth		Review: clinical features	
Georgia			
(4363) Vamable	1M	frozen section	

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Iowa			
(4073) Petersen	100 gender?		surgical treatment
(4350) McNamara	2M; 1F	Review: etiology	
(4731) Drown	6 gender?		necropsy
Illinois			
(4024) Bloch & Bogardus	88 gender?		roentgen therapy
(4053) Kirschbaum	1F	heavy houseworker	pathological conference
(4082) Shapiro	1M		cerebral metastases
(4088) Stein		Review: clinical diagnosis	
(4089) Steiner	21 gender?		roentgen therapy
(4098) Shapiro	1M		clinicopathological report
(4141) Halpert	74 gender?		32 squamous; 23 reserve cell; 10 columnar cell
(4160) Olin	28M; 10F		early diagnosis
(4217) Adams et al	3M; 2F		malignant adenoma
(4219) Behrents	1M		pulmonary arterial thrombosis
(4262) Stein	15M	steel inspector, mail clerk grain broker, truck driver barber, insurance agent, cook gardener, laborer, postman	apical cancer
(4266) Volk et al	1M		clinicopathological report
(4473) Steiner	121 gender?		
(4513) Bloch et al	91 gender?		roentgen diagnosis all white except 1 negro and 1 Filipino, silicosis, delay in diagnosis, alveolar cell tumor, Ayerra's disease
(4533) Holinger et al	157M*; 23F	40 heavy smokers, 14 non-smokers, 126 no information	
(4814) Bates & Ariel	18M		
(4947) Laipply & Fisher	1M; 1F		
Kansas			
(4953) Miller		Review: cytologic diagnosis	
Louisiana			
(3666) Ochsner & DeBakey	15 gender?		amebiasis
(3970) DeBakey & Ochsner		Review: clinical features	
(3981) Ochsner & DeBakey	36M; 15F		pneumonectomy
(4044) Halpert	86M; 6F		38F and 1M were negroes
(4045) Halpert & Pearson			49 squamous cell, 17 columnar cell, 26 reserve cell
(4067) Ochsner & DeBakey	19 gender?		surgical treatment
(4142) Halpert	123M; 12F		necropsy
(4143) Halpert		Discussion: etiology	
(4163) Ochsner & DeBakey		Review: clinical features	
(4164) Ochsner & DeBakey		Review: etiology and clinical features	
(4250) Ochsner & DeBakey		Review: metastases	

Maryland			
(3342) Rienhoff	2 gender?		pneumonectomy
(3788) Rienhoff	16 gender?		pneumonectomy
(4466) Ochsner et al	44 gender?		pneumonectomy
(4555) Ochsner et al	166M; 24F		pneumonectomy
(4556) Ochsner		Review: etiology	
(4557) Ochsner et al		Review: clinical features	
(4635) Horn	40M; 5F		clinicopathologic report
(4651) Ochsner		Review: antismoking literature	
(4772) Ochsner et al	356M; 56F		pneumonectomy
(4773) Ochsner et al	129 gender?		pneumonectomy
(4867) Ochsner et al		Review: pneumonectomy	
(4868) Ochsner et al	426M; 63F		pneumonectomy
(4869) Ochsner et al		Review: pneumonectomy	
(4870) Ochsner et al		Review: clinical features	
(4871) Ochsner et al		Review: clinical features	
(4872) Ochsner et al	548 gender?		64% operable, 35% resectable
(4946) King & Ford		Review: neurological complications	
(4969) Swan	8M* 1F	fertilizer plant worker driver, heavy smoker	adenomatosis
Massachusetts			
(3787) Overholt		Review: pneumonectomy	
(4070) Overholt	104 gender?		21% resectable, 11% 5-year survival
(4097) Overholt	54M; 21F		surgical treatment
(4127) Betts		Review: bronchoscopy	
(4132) Cotton	1M; 1F		differential diagnosis
(4162) Overholt		Review: surgical treatment	
(4216) Adams		Review: pneumonectomy	
(4237) Holmes	163 gender?		93 squamous, 23 adenocarcinoma, 29 oat cell, 13 undifferentiated
(4242) King et al	1M	bartender	clinicopathologic report
(4251) Overholt	153 gender?		surgical treatment
(4255) Pittman	1M		clinicopathologic report
(4318) Adams	5M	metal buffer, farmer, clerk, plumber, salesman	pneumonectomy
(4328) Currens et al	11M; 1F		cardiac arrhythmias
(4341) Jones et al	1F		cat scratch
(4356) Overholt	165 gender?		80 epidermoid, 28 adeno-carcinoma, 57 others
(4443) Hardwood et al	1M	machinist	clinicopathologic report
(4481) Zamecnik et al	1F		recurrent laryngeal nerve paralysis
(4550) Mendeloff	2F	factory worker, salesgirl	asthma
(4811) Adams	182 gender?		post-pneumonectomy survival

obtained by us in rabbits, by a superficial painting of their ears' skin with tar, each 2-3 days, without any other factor interfering." page 115, (4313)

Flory, a pathologist from the University of Chicago, repeated Roffo's ear painting experiments with the following results:

"Twelve rabbits were painted on the ears with a tar produced by the destructive distillation of tobacco at from 350-700°C. Between the 49th and 79th day all rabbits developed tumors at the painting site. The rabbits lived from 238 to over 600 days. Sixty-eight of the tumors examined histologically were papillomas, and 5 were carcinomatoid tumors. No carcinomas were produced. A 130-150°C. destructive distillate tar produced tumors in 16 out of 17 rabbits, but more slowly than the 350-700°C. tar. Forty of these tumors were papillomas and 5 carcinomatoid tumors.

Twenty-four rabbits were painted with tar obtained by smoking tobacco in pipes. Tumors were produced in from 37 to 374 days in 22 out of the 24 rabbits. Seven animals have lived over 640 days. Thirty-six tumors examined histologically were papillomas and 2 were carcinomatoid tumors. No carcinomas were produced.

What then is the status of these carcinomatoid tumors? In this work with tobacco tars evidence does not indicate what the ultimate fate of these tumors would have been. Most of the tumors were identified only at autopsy, although some were seen very early in the painting period. It is of importance to note the absence of definite metastases in all 11 animals with carcinomatoid tumors. It was not proved that such tumors could produce distant metastases. In view of the work of Rous and Kidd it would seem likely that the invasive behavior of these tumors depended on the repeated application of an extrinsic stimulus rather than on an intrinsic capacity for unrestricted growth. There is no evidence that the production of these carcinomatoid tumors in rabbits is an indication of carcinogenic activity of the tobacco tars." page 274, (4037)

Although Flory specifically denied carcinogenic activity, Roffo interpreted the negative result in the opposite way (4276), as did Harris in his SOA report.

(4822) Churchill		Review: clinical features	
(4956) Overholt & Schmidt	721 gender?		early diagnosis
Michigan			
(3756) Brines & Kanning	63M; 5F		17 Polish, 5 Russians, 4 Austrians, 4 Jugoslavs
(4046) Hammond	32M; 8F		early diagnosis
(4813) Ballantine & Byron	1M		cerebral metastasis
(4816) Black	1M		cardiac metastasis
(4847) Levitt	85M; 15F		exploratory surgery
Minnesota			
(4068) Olds & Kirklin	162M; 44F		92 squamous, 111 adeno-carcinoma, 3 mixed
(4069) Olds	(same)		
(4144) Harrington		Review: surgical management	
(4145) Harrington		Review: pneumonectomy	
(4169) Simons		Review: etiology	
(4272) Harrington		Review: pneumonectomy	
(4345) Kinsella	1M		five-year cure
(4351) Moersch & Tinney squamous	370M; 78F		45% adenocarcinoma, 52%
(4352) Moersch & Tinney		Review: early diagnosis	
(4421) Brindley	34M; 11F		surgical treatment
(4425) Clagett & Brindley	(same)		surgical prognosis
(4442) Harrington		Review: pneumonectomy	
(4460) Moersch		Review: diagnosis	
(4477) Tinney		"cigarette cough"	
(4523) Fair & Clagett	1M; 1F		surgical treatment
(4538) Ikeda		Review: alveolar cell tumor	
(4548) McDonald et al	17M; 6F		hematoma
(4566) Samper & Clagett	1M		actinomyces tongue
(4768) Mandell		Review: clinical	
(4832) Good	6M		early diagnosis
(4951) McDonald & Woolner		Review: sputum cytology	
Missouri			
(3665) Glenn		Review: clinical features	
(4129) Bondurant	1M		negro
(4271) Womack & Graham abnormalities	3M; 1F		developmental
(4528) Goldman	1M		pneumonectomy
(4529) Graham & Womack		Review: differential diagnosis	
(4740) Graham		Review: surgical treatment	
(4815) Bergmann et al	3M	coffee peddler	differential diagnosis
(4915) Ackerman		Review: diagnosis	
(4936) Goldman	1M		pleural effusion
(4937) Graham		Review: surgery	

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Nebraska			
(4128) Bisgard	1M	farmer	pneumonectomy
(4784) Simonds & Anderson		Review: treatment	
New Jersey			
(3553) Dieffenbach		Review: clinical features	
(4028) Casilli & White	2M; 1F	dogbreeder, postmaster	bronchial adenoma
New York			
(2959) Karnan & Cracovaner	1F		bronchoscopy
(3047) Martin & Ellis	5 gender?		needle biopsy
(3341) Kerman	4M; 4F		radon implantation
(3670) Wasch & Epstein	39M; 15F		roentgenologic classification
(4023) Biederman	2M	bricklayer, window cleaner	
(4032) Craver	175 gender?		sputum cytology
(4075) Rabinovitch et al	40 gender?		4 squamous, 31 cylindrical, 17 undifferentiated, 14 adenocarcinoma
(4124) Bereston & Ney	1M; 1F		osteomyelitis
(4151) La Fuente & Palacios	1M	waiter	tuberculosis
(4161) Ornstein & Epstein	26 gender?		classification
(4171) Thompson		Review: surgical treatment	
(4173) Ulmer & Auerbach	1M*	watchman, ex-smoker	Russian
(4270) Wessler & Rabin	36 gender?		neurological complications
(4273) Neuhof	5M; 2F		pneumonectomy
(4353) Murray		Review: clinical features	
(4362) Stout	20 gender?		bronchial adenoma
(4368) Wood	1F	housemaid	adenomatosis
(4458) Mitton & Hardisty	88M; 12F		diagnosis
(4516) Chamberlain & Gordon	5M; 5F		
(4647) Neuhof	1M; 1F		cylindroma
(4713) Aufses	1F		slow growth
(4747) Hankin	32M; 4F		metastases
(4754) Humphreys	106M* 16F		42 operable, 29 resectable
(4863) Neuhof & Aufses	52 gender?		pneumonectomy
(4883) Silverman & Angrist	2F		adenocarcinoma
(4916) Auerbach	46M; 4F		grouping by location
(4938) Hayes		Review: symptomatology	
North Carolina			
(4259) Seay	8M; 1F		irritation theory
(4819) Bradshaw		Review: etiology and clinical features	
Ohio			
(4038) Freedlander & Wolpaw	3M; 1F		differential diagnosis
(4052) Jones et al	13 gender?		surgical exploration
(4125) Berghausen	6M	laborer, hatter, mechanic manufacturer, night watchman	clinical reports

(4226) Freedlander & Greenfield	2F		metastatic cancer
(4343) Johnson & Reinhart	57M; 9F		necropsies
(4344) Karsner	1M		nasal metastases
Oklahoma			
(4131) Chont	1M	farmer	bronchial asthma
(4929) Fair		Review: surgical treatment	
Oregon			
(4552) Moore	2M; 2F		bronchial asthma
(4718) Berg et al	65M*	4 nonsmokers	
Pennsylvania			
(4029) Chamberlain	2M; 1F		differential diagnosis
(4060) Mahor & Staderman	30M	occupation not important	necropsies
(4227) Freedman & Bosse	1F		multifocal cancer
(4253) Perrone & Levinson	95M* 20F	1 nonsmoker	no negroes
(4342) Johnson	16M; 4F		pneumonectomy
(4436) Freedman et al	23M; 7F		early diagnosis
(4469) Schnabel		Review: clinical features	
(4554) Muller & Miller	67 gender?		surgical treatment
(4615) Clerf & Herbut	303M; 33F		bronchioscopic diagnosis
(4632) Herbut & Clerf	38 gender?		bronchioscopic cytology
(4633) Herbut & Watson	16M; 1F		Pancoast syndrome
(4831) Gibbon et al	50M; 6F		surgical exploration
(4865) Norris	310 gender?		bronchioscopic diagnosis
(4866) O'Keefe	131 gender?		delayed diagnosis
(4920) Burnett et al	67 gender?		post pneumonectomy
(4922) Clerf & Herbut		Review: bronchospic diagnosis	
(4962) Ryan & Meyer	111M	pathologic classification	
South Carolina			
(4096) Coleman	18 gender?		pneumonectomy
Tennessee			
(4241) Johnson & Daniel		Review: clinical features	
(4256) Quinland	3M	machinist	negroes
Texas			
(4047) Hanks		Review: etiology	
(4095) Tripoli & Holland	171M; 24F		needle puncture biopsy
(4135) Diamond	20 gender?		clinical diagnosis
(4364) Wallace & Jackson	26M* 2F	8 heavy smokers, 6 moderate, 1 nonsmoker, 12 no data	
(4876) Quick & Brindley	44M; 4F	"cigarette cough"	negroes
(4955) Moyer & Ackerman		Review: clinical features	
(4974) Wallace		Review: cytologic diagnosis	

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Virginia			
(4049) Higgins -	25M; 5F	Review: etiology	
(4724) Coleman	79M; 9F		surgical treatment
(4725) Coleman	6M; 1F	farmer, painter	surgical treatment
(4952) Mank & Myer	5M; 1F	truck driver, coal miner farmer, locomotive fireman	histochemical lipase
Washington			
(4146) Hershberger	16M*	12 smokers 10 alcohol drinkers	
Wisconsin			
(2734) Ochsner & Nesbit	1M		pulmonary abscess
(3656) Rice	18M; 12F	8 housewives, 4 laborers 3 farmers, 3 metal workers 1 locomotive fireman	
(4829) Gale & Curreri		Review: surgical indications	
Australia			
(3638) Harvey	87M; 13F		38 exposed to noxious inhalation
		25 outdoors	
(4077) Robb	1M		Russian Jew
(4269) White	1M		traumatic pneumothorax
Canada			
(4031) Corbett	2M		diagnosis
(4175) Whiteside	1F		pneumonectomy
(4783) Simon	1M		alveolar cell cancer
(4858) Madore	72 gender?		15 squamous, 6 adeno-carcinoma, 35 undiff-erentiated
China			
(4050) Hsieh et al	14M; 7F	cook, peanut peddler, clerk, railway employee, merchant, physician, farmer	clinical reports
Denmark			
(4434) Engelbreth-Holm	7M; 5F		bronchial adenoma
Great Britain			
(4078) Roberts		Review: treatment	
(4139) Foster-Carter	12M; 10F		bronchial adenoma
(4157) Mason		Review: clinical features	
(4223) Chandler		Review: clinical features	
(4257) Robertson	12M; 10F		clinical features
(4329) Davidson		Review: differential diagnosis	
(4336) Harnett	69M* 18F	40% male smokers, 33% female smokers	

(4355) Barnard		Review: pathologic features	
(4359) Smart		Review: clinical features	
(4360) Stewart & Allison	1F		bronchiectases
(4431) Dorner et al	1M		Pancoast tumor
(4445) James & Pagel	2M		Pancoast tumor
(4782) Sellors et al	130 gender?		surgical treatment
(4820) Brock	101 gender?		surgical treatment
(4950) Mason	902M; 98F		38% male epidermoid, 11% female epidermoid
Italy			
(4168) Guarnerio & Cambria	9M		differential diagnosis
Japan			
(4065) Murakami	1M		roentgen diagnosis
New Zealand			
(4225) Cronin	1M	motor engineer	case report
Russia			
(4137) Farberov & Baslow	12M; 9F		roentgen therapy
(4656) Shik	116M; 22F		15.6% of all cancer

* Smoking habits recorded

Questionable Increase Incidence in Lung Cancer

The debate as to whether the increase in lung cancer incidence was real, apparent, or both, continued during the 1940's. The most informative literature review was by Willis in his monograph entitled *Pathology of Tumours*:

> "Whereas up to the second decade of this century, carcinoma of the lung was regarded as a relatively rare disease, it is now recognized as one of the commonest forms of cancer, accounting for between 5 and 15 per cent of cases of carcinoma in most recent necropsy series. Is the increase real or only apparent? Attempts to answer this question have reached contradictory conclusions. Having read many of the contributions to the controversy, and having surveyed my own experience on the diagnostic errors made in this disease, my opinion is that it is not possible either to affirm or to deny that there has been a real increase. My reasons for this non-committal opinion are briefly as follow:
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> (a) **Clinical misdiagnoses**, even with all modern diagnostic facilities, are still made in a high proportion of cases. Between 1931 and 1944 I performed 84 necropsies on cases of pulmonary carcinoma, all in a major general hospital; of these, 35 (42 per cent) had been misdiagnosed, 19 as some other kind of malignant disease and 16 as non-neoplastic diseases. Clearly then, the mortality statistics of lung cancer are of dubious value.
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> (b) **Pathological misdiagnoses** are still made in not a few cases, and until the last two decades they were very common. Let anyone who doubts this look up some of the standard pathological journals for the later decades of the nineteenth century, and study the many records of 'mediastinal sarcoma', 'lymphadenoma', 'pleural or pericardial endothelioma', etc. In the light of what we now know of the structure, spread and misleading symptomatology of bronchial carcinomas, the correct diagnosis of many of the cases so recorded will be plain. It is of course now well recognized that most of the erstwhile 'mediastinal oat-cell sarcomas' are secondary deposits of bronchial carcinoma. It is still not sufficiently recognized that secondary growths in the pericardium, pleura or cervical lymph glands may easily be mistaken for primary tumours; and that other errors of pathological diagnosis are being made by those who are unaware of the structural versatility of bronchial cancer and

the ease with which small primary growths may escape detection at necropsy.

(c) Modern diagnostic methods, especially radiography and bronchoscopy, must have brought about, not only **improved diagnosis of lung cancer, but an increasing general acquaintance with the disease and its behavior.**

(d) Pulmonary carcinoma will, of course, have shared in the general increase of cancer because of the **increased proportion of old people in the population.** Comparison of early and recent necropsy series as regards the frequency of lung cancer have often failed to take account of the age compositions of the respective series. Since the disease is much commoner in men than in women, allowance must also be made for the sex ratios of necropsy series to be compared.

(e) Of significance are the **analyses of necropsy** records made by Bonser and by Passey and Holmes. Bonser's analysis of the necropsies during 41 years at Leeds, where an unusually high proportion of fatal cases were examined, showed no increase in the incidence of intra-thoracic cancer when considered with respect either to the total number of necropsies, the total number of cancer cases, or the total number of admissions to hospital. Passey and Holmes studied the incidence of intra-thoracic cancer in the necropsy records of 16 major teaching hospitals in Great Britain; in 8 hospitals there was no evidence that this was increasing, in 3 the results were inconclusive, while in 5 institutions which did show an increase there were special circumstances which may have been responsible. Sitsen and Steiner also are among the many pathologists who deny that there is any satisfactory evidence of a real increase in the incidence of lung cancer during recent years. The suspicion is that where such increase has appeared to have been conspicuous, there was formerly a low standard of accuracy of pathological diagnosis and that the standard has improved with the passage of time.

For the foregoing reasons, comparisons of early and recent clinical or necropsy estimates of incidence, or comparisons of the findings in different countries or in different hospitals, must be quite unreliable. So much depends on the personal experience of the clinicians and pathologists concerned, and current journals contain evidence enough that a uniformly high standard of diagnosis of this elusive disease has not yet been attained by either. Now that the properties of the disease are becoming better known, however, its true frequency and trend in a given community or institution

thousand cases in Canada (4646); and Rosahn, based on 86 autopsies performed at Yale University School of Medicine (4079). The latter reviewed factors which might have been responsible for the increase such as improved clinical and pathologic methods of diagnosis, increased attention to lung cancer, increase in span of human life, and no comparable increase in tumors of the skin.

Boyd, a Professor of Pathology from the University of Toronto, reviewed the reasons for the recent increase in lung cancer. He suggested that the greater part of the increase was apparent and was not prepared to "go so far as to state that none of it is real."

> "We have seen that the most important factor in the recent increased incidence of bronchial carcinoma is its better recognition. This is true for the clinician, radiologist and pathologist. The eyes of the first two have been opened by the observations of the pathologist. The latter has been misled in the past for three principal reasons. (1) It is easy to overlook the bronchial origin of the gross lesion, in which case the tumor is apt to be regarded as a metastatic one. (2) These tumors may closely mimic sarcomas and lymphosarcomas, and very many of the cases in the past have been wrongly labelled as such lesions. (3) The natural history of the disease as illustrated by the behavior of the metastases is highly characteristic, but the knowledge of this truth is of recent date. It is suggested that various factors which have been discussed coupled with the increase in the span of life are sufficient reason for the apparent increase in bronchial carcinoma." page 13, (4130)

Clinical Diagnosis and Treatment

As indicated in the Tabulated Case Reports, about one-quarter of articles were reviews on clinical features,

differential diagnosis, surgical management, histopathologic classification, and radiation therapy. Surgeons such as Graham from Missouri, Ochsner from Louisiana, and Overholt from Massachusetts, were initially optimistic about pneumonectomy, but towards the late 1940's, it became apparent that the five-year survival rate was just as uncommon as radiation therapy.

There was consensus on the importance of early diagnosis. However, there were conflicting opinions as to whether delay in treatment was due to patients' or physicians' unawareness of signs and symptoms to assure early diagnosis. In a survey conducted by Bates & Ariel at Veteran's Hospital at Hines, Illinois, although 18 lung cancer patients were given definitive treatment, 5 favored to confer with their doctor within three months of onset and 14 cases were not provided treatment within 3 months of first visit, and 2 cases of delay decided by both patient and physician (4814). There was a necessity to educate the general public on early symptoms of lung cancer and to encourage physicians to exclude the disease in differential diagnosis of chest signs and symptoms. There were articles advising young physicians to improve history taking and physical examination for diagnosis of lung cancer (4897). There was no mention of cigarette smoking as a potential cause.

C. CIGARETTE SMOKING AND LUNG CANCER

The literature on tobacco use and lung cancer became more specific during the 1940's. Unlike earlier decades, publications just prior to 1950 separated the health effects of cigarette smoking from those of pipe and cigar smoking and tobacco chewing. Characterization of smoking habit detailed only as far as whether the individual was a non-smoker or cigarette smoker, and occasionally a heavy smoker. The number of cigarettes consumed daily was rarely specified and the manner of inhaling cigarette smoke was not mentioned in medical publications.

Research on health effects of cigarette smoking was usually conducted by physicians. Prior to 1950, there was hardly any non-medically trained scientist who conducted health research because doctorates in biochemistry, physiology (and other medical sciences) were rare. Lung cancer research conducted by physician-researchers was criticized by those who had non-medical degrees, particularly, chemists, biologists, epidemiologists and public health workers. The publications discussed below were written mostly by physicians, except those under the subtopic of chemical constituents of cigarette smoke, contributed by chemists. Articles on composition of cigarette smoke published during the 1930's are transferred from Chapter III and included below together with those published during the 1940's.

Lung Cancer Monographers

As stated in the Introductory List of Lung Cancer Monographers, Fried continued to question any causative role of tobacco: "Evidence thus far adduced is contrary to the idea that bronchiogenic cancer is caused by tobacco" (see above, pages 428 and 429 for detailed quotation **(4801)**. Willis reviewed the role of carcinogenic hydrocarbons with special reference to tobacco smoke.

> "Experimental investigation, has shown that the incidence of lung tumours in mice can be markedly increased by the administration of carcinogenic hydrocarbons by inhalation or by subcutaneous, intraperitoneal or intravenous injections. The possibility must, then, be conceded that exposure of human beings to such substances may be a factor in the causation of lung cancer; and that, while inhalation is clearly the most likely mode of introduction of such agents, absorption by other routes must also be considered. **Tar, oil, soots, tobacco smoke and other smokes, must all be arraigned; but clearly, proof of either the culpability or innocence of any particular material will not be easy to establish.** Such proof will entail (a) demonstration of the presence of carcinogenic substances in the suspected material, (b) evidence that the material is inhaled or otherwise absorbed by exposed persons, and (c) evidence that habitually exposed persons do show an excessive incidence of lung cancer, and that this excessive incidence is reduced by eliminating the suspected risk. While the first step (a) has already been accomplished for many of the suspect materials, scarcely any of the evidence (b) or (c) has been obtained, and it will be very difficult to obtain.
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> For example, suppose that tobacco smoking *is* an important cause of lung cancer and that it acts by producing chemical carcinogens which are inhaled. It may be easy to identify the carcinogens in tobacco smoke or tar, but it may be difficult to prove that they are effectively inhaled, even more difficult to group patients correctly according to their present and past tobacco consumption, and probably impossible to prevail on any large group of men of homogeneous occupation to renounce smoking for life so that the ultimate incidence

of lung cancer in them (proved by necropsy) may be compared with that of their smoking fellows. **Comparisons of the smoking habits of victims of lung cancer with those of control cases obtained by careful questionnaires, like Muller's, afford strong grounds for suspecting the carcinogenic results of smoking; but, however strongly suggestive, they cannot afford incontrovertible proof - especially in the eyes of smokers themselves!** Proof of the harmfulness of inhaled domestic and industrial soots and smokes or of dust from tarred roads, to which all persons in urban populations are almost equally exposed, will be even more difficult to secure." pages 363-364, **(4802)**

During the 1950's, Alton Ochsner wrote a brief monograph on lung cancer (See Chapter V). For two decades prior to its publication, Ochsner wrote on the subject. Although the articles were largely on the subject of surgical management of patients with lung cancer, Ochsner, DeBakey and their collaborators from Charity Hospital of New Orleans, reviewed etiology and clinical diagnosis. In publications be-tween 1939 to 1948, Ochsner's changing opinion on causative role of cigarette smoking was reflected by the following quotations:

(3970) DeBakey & Ochsner

"The inhalation of irritating gases, such as war gas, exhaust gas of combustion motors, and gases arising from tarred roads, have been suggested as etiologic factors. The high incidence of carcinoma of the lung among workers in the Schneeberg mines has long been known. Investigations of these mines revealed that the air within these mines contained radio-active particles as well as a high content of arsenic and cobalt, and several investigators have expressed the opinion that the high incidence of primary lung malignancy among these mines is due to the radio-active factors. In a previous publication the authors have emphasized the possible etiologic relationship between the increase in smoking and the increase in pulmonary carcinoma. The irritating carcinogenic effects of tobacco have been repeatedly demonstrated. Roffo, on the basis of exten-

sive clinical and experimental observation, concluded that tobacco is one of the most important carcinogenic agents, and has been able to produce tumors in rats experimentally as easily with tar obtained from tobacco as with coal tar. **During the period, 1920-1936 inclusive, the authors observed a significant relationship between the increased incidence of cancer of the lung in the United States and the increased production of tobacco."** pages 2524-2526, (3970)

Note: The cited article "In Press in Transactions of American Cancer Society" is not available to me after repeated attempts.

(3981) Ochsner & DeBakey

"Although it is controversial whether the increase in pulmonary carcinoma in recent years is apparent or real, the German autopsy statistics would indicate that the increase is actual and not only apparent. There are several explanations for the actual increase in the incidence of pulmonary malignancies, most of which have not been satisfactory. A number of theories have been suggested. Winternitz, Watson, and McNamara, because of the presence of metaplasia in the bronchial mucosa of persons dying from influenza, suggested that this change is a precancerous lesion. The inhalation of irritating gases such as war gas or gas originating from the increased use of motor cars has been proposed as an etiological factor. **In our opinion the increase in smoking with the universal custom of inhaling is probably a responsible factor, as the inhaled smoke, constantly repeated over a long period of time, undoubtedly is a source of chronic irritation to the bronchial mucosa.** In addition to the actual increase in pulmonary malignancy, there is unquestionably a relative increase in those localities where routine postmortem examinations previously have not been made. This is due probably to the fact that the condition has not been suspected in many cases and adequate diagnostic procedures have not been employed. The recent development of thoracic surgery has stimulated interest in intrathoracic lesions. This, with the development of specialized methods of diagnosis, has facilitated the recognition of pulmonary malignancies.

Summary: Chronic irritation of the bronchial mucosa is probably the most important etiological factor. Repeated inhalation of smoke over long periods of time is believed to be a prominent, irritating factor." pages 435-436, (3981)

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(4163) Ochsner

"The probable significance between the increase in smoking and the increase in pulmonary malignancy has been previously emphasized by the authors. Numerous investigators have repeatedly demonstrated the irritating carcinogenic effect of tobacco. Roffo, on the basis of his extensive investigations, is convinced that tobacco is one of the most important carcinogenic agents. He has been able to produce tumors in rabbits as easily with tobacco tar as with coal tar. Hoffmann is 'strongly of the opinion that a relation between in increase in smoking habits and cancer of the lung may be safely assumed to exist.' We found a significant relationship between the increased incidence of carcinoma of the lung in the United States and the increased production of tobacco." page 389, (4163)

(4164) Ochsner & DeBakey

"In a previous publication we called attention to the possible etiologic relation between the increase in smoking, with the universal custom of inhaling, and the increase in pulmonary carcinoma. The inhalation of smoke constantly repeated over a long period produces a chronic irritation of the bronchial mucosa, as is evinced by the characteristically associated cough. As early as 1923, Fahr stated that in his opinion the increase in the incidence of pulmonary carcinoma was due to the increased incidence of cigarette smoke. Lickint also expressed the opinion that the inhalation of tobacco smoke is a responsible factor in the increase of bronchogenic carcinoma and that such carcinoma in many cases can be prevented by abstinence from smoking, particularly by patients belonging to families known to have a high cancer incidence. Tylecote stated: 'In almost every case I have seen and known of the patient has been a regular smoker, generally or cigarets.' McNally expressed the opinion that the tar of cigarette smoke may account for the recorded increase of cancer of the lung. Mertens has also expressed this view. Bogen and Loomis stated that the only woman with cancer of the lung on whom autopsy was done at the Olive View Sanatorium had smoked cigarets excessively for more than fifteen years.

It is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking, particularly cigarette smoking, which is universally associated with inhalation. Every one of our patients, with the exception of 2 women, was

an excessive smoker. Of particular interest in this connection is the comparison of the death rate per hundred thousand of population from cancer of the lung with the production of tobacco and automobiles in the United States during the seventeen year period 1920 to 1936 inclusive. It may be observed from a graphic representation of these incidences that, **whereas there is no significant relation between the production of automobiles and cancer of the lung, there is an obvious parallelism between the increased production of tobacco and carcinoma of the lung."** pages 219-221, (4164)

Note: All citations by Ochsner were collected and six were reviewd in Chapter III.

(4468) Ochsner, Dixon & DeBakey

"Whereas there are a number of factors which are responsible for the increased incidence of bronchiogenic carcinoma, it is our firm belief, as we have emphasized in previous publications, that the increased incidence is due to the greater frequency of smoking. Inhalation of smoke constantly repeated over long periods produces chronic irritation of the bronchial mucosa as is evidenced by the characteristically associated cough. Experimentally, the carcinogenic effect of tobacco has been demonstrated repeatedly. Roffo stated the conviction, on the basis of his clinical observations of 78,000 patients treated in the University Institute of Experimental Medicine for the Study of the Treatment of Cancer in Buenos Aires, that tobacco is the most important factor in determining the localization of cancer. He was able to produce carcinoma by applying tar derived from various tobaccos. Hoffman, on the basis of his statistical analyses of the incidence of cancer, states, 'Smoking habits unquestionably increase the liability of cancer of the mouth, the throat, the esophagus, the larynx, and the lung. The change in the cancer death rate during recent years has not, however, been at all disproportionate to the enormous increase in cigarette smoking habit which has replaced the older method of smoking, unquestionably, more injurious than smoking cigars. **The increase in cancer of the lung observed in this and many other countries is in all probability to a certain extent directly traceable to the common practice of cigarette smoking and inhalation of cigarette smoke.** The latter factors unquestionably increase the danger of cancer development.'" page 29, (4466)

(4555) Ochsner, Dixon & DeBakey

"We have repeatedly emphasized the probable relationship between smoking and the increased incidence of bronchiogenic carcinoma. The chronic irritation resulting from the inhalation of cigarette smoke over long periods of time is well known and the chronic bronchitis in smokers is so common that their cough is considered inconsequential and of no significance. Whereas prolonged chronic irritation of the bronchial mucosa as a result of inhalation of smoke can in itself be a factor in the production of neoplastic disease just as any prolonged and continued irritation can produce such a lesion, **it is probable that smoking exerts an additional and more active influence than chronic irritation alone.** Experimentally, it has been demonstrated that tobacco exerts a carcinogenic effect." pages 1198-1199, (4555)

(4556) Ochsner

"It has also been suggested that the inhalation of exhaust gases from automobile engines might be a factor in the production of cancer of the lung. We have shown, however, that there is no parallelism between the sale of automobile tags and the incidence of lung cancer. On the other hand, **there is a distinct parallelism between the incidence of cancer of the lung and the sale of cigarettes,** and it is our belief that the increased incidence of lung cancer is due to the increased incidence of smoking and that smoking is a factor because of the chronic irritation that it produces. It is well known that the smoker has a chronic cough, the so-called smoker's cough, which because of its irritation might alone be responsible for the development of lung cancer. However, in addition to this it has been shown by Professor Roffo, Director of the Institute for Malignant Disease in Buenos Aires, tobacco contains a tar which has a carcinogenic effect and that the application of this tar to the skin and the mucous membrane of the respiratory tract in animals will produce cancer." page 105, (4556)

(4557) Ochsner, Dixon & DeBakey

"Etiology: Whereas there are a number of factors which are responsible for the increased incidence of bronchiogenic carcinoma, it is our firm belief, as we have summarized in previous publications, that the increased incidence is due chiefly to the greater

frequency of smoking. The repeated inhalations of smoke over long periods produce chronic irritation of the bronchial mucosa as evidenced by the characteristically associated cough. As early as 1923, Fahr stated that in his opinion the increase in incidence of pulmonary carcinoma was due to the incidence of cigarette smoking. Lickint also expressed he opinion that the inhalation of tobacco smoke is a responsible factor in the increase of bronchiogenic carcinoma and that such carcinoma in many cases can be prevented by abstinence from smoking, particularly by patients whose families have been known to have a high cancer incidence. **That smoking is of etiologic significance has been emphasized by Tylecote, McNally, Mertens, Bogen and Loomis."** pages 101-102, (4557)

(4651) Ochsner

"Although the exact cause of cancer is not known, it is well accepted by medical authorities that chronic irritation over long periods of time will produce changes in the cells which are irritated, and this abnormal overgrowth of cells results in cancer. It is also well known that cigarette smoking with the inhalation of the smoke results in chronic irritation of the bronchial tubes as evidenced by the so-called smoker's cough, and it is reasonable to assume that this irritation alone over many years' time might be responsible for the development of cancer of the lung. **In addition to the chronic irritative factor, cigarette smoking probably exerts an additional more active influence.** Experimentally it has been demonstrated that tobacco can produce cancer, as evidenced by the researches of such men as Wacker and Schmincke, Leitch, Philippson, Lickint, Roffo, Morpurgo, and Boehncke." page 6, (4651)

(4772) Ochsner

"The apparent increase in the incidence of carcinoma of the lung stimulated much speculation concerning its cause. The numerous explanations advanced to account for this fact have been reviewed in previous publications. In the analysis of this series none of those factors was found to bear a significant relation to the occurrence of the disease. **Both occupation and smoking, which have been particularly emphasized by some observers as possible etiologic factors, and which we were inclined previously to consider more seriously, were found to have no special significance in his analysis.** Of the 147 patients in

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whom pulmonary resection was performed 76 per cent were smokers and 24 per cent were nonsmokers, and the number of those who had indoor occupations was almost equal to that of those who did outdoor work." page 322, **(4772)**

(4773) Ochsner, DeBakey & Dixon

"The numerous explanations advanced to account for the apparent increase in incidence in carcinoma of the lung have been reviewed in previous publications and will not be discussed here. In the 129 resected cases no factor was found which might bear a significant relationship to the occurrence of the disease. **Neither occupation nor smoking habits, which some reports, including our own, have stressed as of possible etiologic significance, seemed of any special significance in this particular series** (Charts 5 and 6: 75% smokers and 25% nonsmokers)." page 525, (4773)

(4867) Ochsner

"The cause of bronchogenic carcinoma is not known. There is some presumptive evidence that smoking might be a factor and might account for the increased incidence. It is conceivable that the long continued irritation of the bronchial mucosa caused by habitual smoking may be an etiologic factor." page 43, (4867)

(4871) Ochsner, DeBakey & Richman

"The etiology of bronchogenic carcinoma is unknown, aside from the fact that males are much more frequently involved than females, which permits the conclusion that there is a greater predisposition in the male. On the other hand one cannot say what the cause is of the increasing incidence of this type of malignant process. **Although we previously were of the opinion that the chronic irritation resulting from excessive cigarette smoking was a factor, this cannot be proved.** However, the fact that there is a parallelism between the number of cigarettes sold in the United States and the increased incidence of bronchiogenic carcinoma is interesting." page 596, (4871)

The changing opinion on the role of cigarette smoking can be derived from references **(4772)** (4867) and (4871). Ochsner concluded that both occupation and smoking had **"no special**

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included in the following checklist of 35 articles.

(4046) Hammond; Detroit, MI; G466

"In the present series the male sex predominated, there being 32 men to 8 women, or a ratio of 4 to 1. This high male incidence may be explained perhaps on the basis of indulgence in tobacco. Roffo in 1936 produced definite experimental evidence that tobacco has carcinogenic properties and that the cancer which occurs in smokers in the tissues of the lips, oral cavity, tongue, respiratory tract and lungs may be traced to the excessive us of tobacco. He found that the distillation and combustion products of tobacco, especially the tar, when applied daily over a long time on rabbits' ears, led in 95 per cent of the animals to the production of papillomas, which after nine months had degenerated into squamous cell carcinomas. Furthermore, he determined that a heavy smoker who consumes, for example, three packages of cigarets per day, deposits 400 Gm. of tar per year, or nearly 10 pounds in ten years, on the mucosa of the oral and the respiratory system. That the continuous irritation from such large amounts of tar deposits must necessarily have a carcinogenic effect also in the human body appears reasonable enough. It has been suggested, especially by Weller, that other irritative factors, such as chemical, mechanical, bacterial, thermal and radioactive agents, might play an etiologic role in the production of carcinoma of the lung, but the influence of these factors in the present series was less apparent. **The only exceptions may be represented by the 2 cases, 1 of a man and 1 of a woman, in which bronchiectasis of over eight years' duration preceded the onset of the carcinoma."** page 781, (4046)

Note: Although Hammond cited smoking references, he did not publish smoking habits of his own series of 40 lung cancer patients.

(4047) Hanks; Sanatorium, TX; G555

"The etiology of primary carcinoma must be considered as dependent upon the same conditions that produce carcinoma elsewhere in the body. In common with all cancer, many theories have been advanced to account for its origin. **All authors agree on one point, however, and that is irritation of the bronchial mucous membrane.** Influenza has been advanced as a causative factor in the formation of this malignant condition. The basis for this accusation probably is that influenza causes a change of the normal columnar epithelium to a stratified

squamous epithelium which is more easily excited to hyperactivity and therefore malignancy. **Poison gas, tar and use of tobacco have received their share of the blame for this disease due to the irritant properties they contain."** page 2597, (4047)

(4049) Higgins; Richmond, VA; G555

"Closely linked with the possible role of tar is the evidence against tobacco. The recent sale of a cigarette holder which encloses a cigarette through which the smoke is filtered is a graphic demonstration of the amount of tar resin introduced into the bronchial passages in the course of a day. **The incidence of smokers in some series is remarkably high although Vinson noted the fact that only seventy of 140 cases of carcinoma of the tracheobronchial tree, at the Mayo Clinic, were smokers. Tobacco smoke as a lung irritant may be considered at least a possible cause of pulmonary malignancy in susceptible individuals but not necessarily a major factor.** In any event, all known etiologic agents have in common the one characteristic of producing pulmonary irritation and, since they are so diverse, the only conclusion possible is that such irritation is the real activating or causative factor in the disease. Simons asserts that the reduction of all the present known facts to one formula is a positive result of the work so far performed." page 363, (4049)

(4059) Macklin & Macklin; London, CAN; Z566

"Other agents, such as roentgen rays, tobacco smoke and motor exhaust fumes, have been suggested as possible causes. The suggestion that roentgen rays are a cause is almost absurd, for the probabilities are that only a small percentage of those in whom cancer of the lungs has developed ever had their chest under roentgen rays before they came for diagnosis of their cancer. Motor mechanics working in garages where there is an abundance of exhaust fumes are said to show no higher incidence of pulmonary cancer than the general population, and Campbell stated that exhaust gases from internal combustion engines do not increase pulmonary cancer in mice. Tobacco smoke might be one factor in the increase of pulmonary cancer. The habit is one which permits long-continued use application of the smoke to the bronchial mucosa; it is, or at least was, a habit more prevalent among men; there are two possible agents which might prove to be cancer producing, namely, heat and the derivatives of tobacco. There are those who point out

that the increase in the consumption of tobacco parallels the increase in the incidence of pulmonary cancer. This may or may not have significance. If tobacco is a factor, it must be proved that derivatives of tobacco are carcinogenic or that the repeated application of heated smoke is conducive to cancer. McNally stated that the tar in cigarette smoke contains enough chemical irritants to account for the increase in cancer of the lung. Roffo found among a group of 5,000 cancerous women 42 who exhibited cancer in what he called the 'smoke stream' namely, the lips, tongue, jaws, larynx and pharynx. All of these women were heavy smokers. He found that the products of burnt tobacco produced carcinoma when painted on rabbit ears, and he feels that there are probably many aromatic substances in tobacco that are carcinogenic. His findings are suggestive. But the increase in cancer of the lung should be much greater among females than among males, since smoking has increased among women far more rapidly in the last two decades than it has among men. Data published by the Metropolitan Life Insurance Company show that the incidence is not greater among females. The rates among the industrial policyholders of 45 to 74 years of age show that in 1917 the rate for pulmonary cancer among females was 2.5 per hundred thousand. This rose to 8 per hundred thousand in 1938, an increase of 220 per cent. The rate for cancer of the lung in males rose in the same period from 3.2 to almost 23 per hundred thousand, an increase of more than 600 per cent. Their conclusion is that it appears doubtful that smoking is a factor in causing cancer of the lung.

Controlled observations over a longer period are necessary to settle this point. Investigators must not rest content with finding that a high percentage of patients with pulmonary cancer are tobacco smokers; they must find that the percentage of smokers in this group is significantly higher than that in the general population of a similar age and sex distribution.

When we review all the theories on the cause of pulmonary cancer, we find that not one supposed cause has been proved to be a real cause and that none of the alleged causes has been investigated with sufficient statistical accuracy to enable the observer to pass an opinion carrying any weight. No one cause, no sum of causes, no common factor in them, namely, chronic irritation through inflammation of the bronchial mucosa, has been demonstrated to occur with any greater frequency in patients with cancer of the lung than in a group from the general population of comparable age and sex distribution at a time sufficiently long before the

onset of the cancer that it may be interpreted as antedating this rather than following it. Naturally, any condition which is a sequela of cancer of the lung may be found more frequently in patients with pulmonary cancer than in persons not affected with this type of cancer. Such a condition when obviously the result of cancer of the lung must be excluded from a discussion of the latter's causes." pages 944-945, (4059)

(4095) Tripoli & Holland; New Orleans, LA; G555

"The etiology of carcinoma of the lung is still not clear. The factors most frequently emphasized include dust, chemicals, gases, fumes and tobacco, as well as such pre-existing diseases as influenza, tuberculosis, and syphilis. The carcinogenic properties of silica and road dust, with and without tar, have been demonstrated in mice by Campbell, and their effects in humans seem to be supported by the reports of Schmorl and of Pirchan and Sikl. **The widespread incidence of influenza, and the equally general use to tobacco, suggest a possible relationship, but the association is not clear, and neither these nor any other factors could be demonstrated as causal in any of the cases in our series."** page 560, (4095)

(4096) Coleman; Columbia, SC; G550

"The increased incidence of cancer of the lung is both relative and real. **The wider use** of coal tar products exhaust gases from automobiles, tobacco smoking, and other agents resulting in chronic pulmonary irritation are **considered to account for the real increase in cancer of the lung."** page 46, (4096)

(4129) Bondurant; Jefferson Barracks, MO; G555

"Hammond cites Roffo who, in 1936, **adduced what he thought was experimental evidence that tobacco is a possible cause of cancer,** and that occurrence of malignant growths of the tongue, lungs, respiratory tract, lips, and oral cavity followed excessive smoking. Roffo reported that applications of the distillation and combustion products of tobacco, especially the tar, when applied daily for a considerable period of time over rabbits' ears, caused papillomas in 95 per cent of the animals; and that these, after 9 months, degenerated into squamous cell carcinomas. He also mentioned that a heavy smoker who consumes, for example, three packages of cigarettes per day, deposits 400 gm. or tar per

year, or nearly 10 pounds in 10 years on the mucosa of the oral and respiratory tracts." page 388, (4129)

(4135) Diamond; Legion, TX; G988

"The nature of the patient's antecedent history offers the physician little aid in his efforts to establish the diagnosis. Some observers are of the opinion that chronic irritation is a major factor in the production of malignant changes in the walls of the bronchi. However, except for the unexplained high incidence of malignant pulmonary neoplasms among Schneeberg miners with pneumonoconiosis, no definite evidence has been adduced in support of this concept. **The actual existence of a significant relationship between the development of cancer of the lung and a previous history of smoking, prolonged exposure to irritating dusts or vapors, or the presence of long-standing bronchopulmonary infection has yet to be shown. Were smoking a factor of any moment, there should have been a marked change in the comparative sex incidence of the lesion in recent years, corresponding to the rapidly growing prevalence of the habit among women.** Instead, the predilection of pulmonary carcinoma for men is as pronounced today as it was thirty years ago. ... Chronic bronchopulmonary irritation prior to the development of neoplasm was not particularly marked among our patients at Legion. Eleven of the men smoked; 8 were moderate smokers, 3 heavy smokers. In none of the cases did the patient's occupation or environment involve the continued inhalation of irritating substances. A history of previous respiratory affection was present in 8 patients: 5, all of whom smoked, had a chronic cough; 1 suffered from asthma; 2 had been through a siege of influenza during the epidemic of 1917. The absence of tuberculosis in these 20 patients with pulmonary carcinomata is noteworthy, for the hospital has an active tuberculosis service of more than 200 beds." pages 713-714, (4135)

(4143) Halpert; New Orleans, LA; G555

"The contribution of Dr. Menne and Dr. Anderson presents evidence that there is a relative as well as an absolute increase in carcinoma of the lung. Their data from the Pacific Northwest on necropsy material are almost identical with those reported by Rosahn from the East and with our own data from the South. Carcinoma of the lung, in fact, is becoming the second if not the first most common malignant neoplasm in the male.

Chronic irritations from infections, inhalation of gases, foreign bodies and particularly smoking of tobacco with its nicotine and tar content may play a part, but perhaps more important is the fact that more people are reaching the cancer age. Whether the gross morphologic classification according to location and extent of the growth as suggested by Dr. Menne and the one by Dr. Karsner have any practical value remains to be seen. At present there are no gross criteria by which the cellular structure can be ascertained without microscopic examination." pages 2221-2222, (4143)

(4146) Hershberger; Seattle, WA; G555

"A review was made of the 16 proved cases seen at this hospital for possible etiological factors. These cases were white males, with the exception of one Negro. The ages on admission ranged from 44 to 70 years, the average age of all patients being 52.5 years. The occupations, according to the histories, were not significant and there was no evidence of exposure to unusual occupational hazards. Concerning their habits, 12 on admission gave a history of smoking, 5 using cigarettes. Ten men stated that they used some form of alcohol. A history of chronic pulmonary disease was obtained from 3 patients; one stated that he had a cough as long as he could remember; another stated that he had asthma and bronchitis for 15 years; the third had symptoms of pulmonary tuberculosis for nearly 5 years, and this diagnosis was made and proved by positive sputum examinations during his stay at this hospital. The Kahn test was positive in only 3 cases and negative in 13 in our own laboratory. That a positive serology can lead to confusion in the diagnosis of this condition is shown in a later paragraph." page 3, (4146)

(4148) Jackson & Jackson; Philadelphia, PA; K400

"From our record we can make the parallel statement that the proportion of smokers among patients with laryngeal cancer is very high. The researches of Roffo on the cancerigenic effects of tobacco are thorough; the results are interesting and important. This etiologic factor is important in relation to the study of incidence because in our experience the proportion of men with cancer of the larynx to women with this lesion is 10:1. Among our patients about 95 per cent of the men were smokers of tobacco; none of the women whose cases were recorded prior to two years ago was a smoker.

Now that smoking among women is becoming deplorably common it will be interesting to note in the future the relative incidence in women. The same may be said of alcohol. Our observations lead us to believe that alcohol used in beverages is a cause of cancer of the larynx. This opinion is strongly supported by the results of investigations by research workers." page 59, (4148)

(4156) Menne & Anderson; Portland, OR; G466

"More recently investigators have turned their attention to the possible influence of the increased use of smoking tobacco (especially the marked increase in the use of cigarets). Myers pointed to the enormous increase in the number of cigarets consumed in this country. In 1880, 582,718,995 cigarets were consumed, in comparison with 169,847,245,964 in 1937. Myers noted also that the toxic products of the combustion and distillation of tobacco are carbon monoxide, ammonia, formaldehyde, methylamine, methane, methyl alcohol, hydrogen sulfide, pyridin, furfural, arsenic and hydrocyanic acid. Of these the nicotine and tar contents are thought to be the most harmful. The former is an irritant of mucous membranes and the latter is regarded as carcinogenic. Myers stated that 'the smoking habits unquestionably increase the liability to cancer of the mouth, throat, esophagus, the larynx and the lungs.' Cramer noted that habitual smoking producing chronic inflammation of the mouth, pharynx, larynx and bronchial mucosa was present among the steel workers studied by him. In comparing the influence of tobacco smoking with that of the gases coming from automobile exhausts, Cramer demonstrated that a 5 Gm. cigar yielded 200 mg. of tar (phenanthrene), while an eight hour drive 10 meters behind an automobile resulted in the collection of only 1.5 mg. of a similar tar. This author appeared to be convinced of the influence of tobacco smoking in the causation of bronchiogenic carcinoma. Roffo stated that 'the tobacco tars are very strong cancer producing' agents and that they are in the 'same form as the coal tars and certain substances whose properties are very like those of the hydrocarbons distilled out of coal in their fluorescence and their spectrometry.' He produced cancers by the application of tobacco tars to the ears of rabbits. He pointed out that 'one can easily see large opportunity of cancerization in a regular smoker who consumes 1 kilogram of tobacco monthly, which means 70 cc. of tar.' In this manner Roffo reasoned that 'the average smoker loads in one year 840 cc. and in ten

years over 8 liters of tar on his buccopharyngolaryngo-pulmonary membranes, which certainly have not the biologic resistance of the skin of a rabbit.' Turner and Willis observed bronchiogenic carcinoma in a gold miner who had influenza and smoked 1/2 pound (226 Gm.) of black tobacco a week.

Certainly the striking predominance of bronchiogenic carcinoma in men as compared with the incidence among women suggests either that in the industries men come in contact with an irritating substance or that the increased consumption (smoking) of tobacco by men as compared with its use by women is of great significance. It would seem that more careful recording of this histories to how much particular persons smoke would be of great value in determining the causal relation of the use of tobacco to bronchiogenic carcinoma. The average inquiry simply elicits information that the patient is or is not a user of tobacco. It is too early as yet to observe in the statistics of the literature the possible influence that tobacco smoking may exert on the incidence of bronchiogenic carcinoma in women who are now smoking cigarets, often more excessively than do men. A report by Rice, although it concerned a small number of patients (18 men and 12 women) seemed to indicate an increase among the women." pages 2218-2219, (4156)

(4233) Harrison; Shreveport, LA; Z666

"War gases have been mentioned but their importance seems to be slight. The same is true of tobacco smoke. **It may be an irritant but it probably is not an important factor. If tobacco were the cause of lung cancer, why has not carcinoma of the lips and tongue increased at a rate parallel with carcinoma of the lung?"** pages 2781-2783, (4233)

(4253) Perrone & Levinsen; Pittsburgh, PA; G955

"The etiological factor here as in other carcinomas is still a mystery. The various factors suggested are heredity, trauma, pulmonary tuberculosis, influenza, pneumoconiosis, chronic pulmonary diseases, roentgen-ray, dust inhalation, tin particles, motor exhaust fumes, war gases, occupational hazards, tobacco smoking. Simons concluded that no single etiologic agent could be pointed out as the cause of pulmonary cancer. He states, **'In any event, all known etiologic agents have in common the one characteristic of producing pulmonary irritation and, since they are so diverse, the only**

conclusion possible is that such irritation is the real activating or causative factor in the disease. This is not to say, of course, that all chronic pulmonary irritations ensue in carcinomas; and it is to be hoped that future research will make this definition of the cause either more specific or more conclusive or both." pages 13-14, (4253)

(4334) Grace; Brooklyn, NY; G205

"After having had an opportunity to observe, over a period of ten years, an unusually large series of patients with cancer of the lung, in two of the large municipal hospitals in New York City, two very distinct elements were noted in these patients: First, they were always men; second, they were heavy cigarette smokers and almost always inhalers. It is obvious, therefore, that this product of combustion deeply inhaled into the lungs of cigarette smokers - for cigarette smokers usually inhale - is deposited in the lung along the entire bronchial system, and most of the biologic principles are present, I believe, to produce bronchogenic carcinoma in accordance with well known animal experiments." (page 361, Harris SOA quotations in Table 2)

"There is no experimental proof at hand to demonstrate that the smoking of many cigarettes was the cause of lung cancer, however, some aspects of this problem should be carefully evaluated." page 361, (4334) omitted by Harris.

(4353) Murray; Brooklyn, NY; G666

"Aside from the knowledge that some form of chronic irritation plays a leading role in the etiology of these tumors nothing really definite is known. Much speculation has been indulged in but nothing actually proven. Simons reviewed exhaustively all possible etiological factors, pointing out that some form of chronic irritation underlay practically all of them. With slight rearrangement these etiological factors are as follows:

1) Chemical - Inhalation of (a) tar particles, (b) motor exhaust fumes, (c) war gases, (d) tobacco smoke, (e) certain dusts (as in pneumoconiosis or in the case of the Schneeberg miners). It is assumed that there has been a marked increase in the above during the past 30 years, coincident with the increase in the incidence of bronchogenic carcinoma.

2) Mechanical - Trauma (19 out of 500 cases).

3) Bacterial - (a) Tuberculosis 15 per cent, (b) influenza (again the increased incidence since the great influenza pandemic of 1918-1919 has been noted), (c) chronic respiratory infections and their sequelae - lung abscess, chronic bronchitis, bronchiectasis (many believe the latter the result rather than the cause).

4) Heredity - 64 out of 930 cases.

All the above may be vital contributing factors but none of them by themselves have been proven conclusively to have produced cancer of the lung. Apparently some constitutional defect, probably congenital, must be present to pave the way for the deleterious effects of chronic irritation." pages 390-392, (4353)

(4364) Wallace & Jackson; Galveston, TX; G177

"We believe that tobacco smoking plays a definite role in the causation of primary lung carcinoma. ... In connection with tobacco smoke we should like to point out the increase in incidence of bronchogenic carcinoma in women in the past several decades and the relationship of this to the increased incidence of smoking in women during this period." page 607, Harris' SOA quotation]

"As in all cancer, there is no known definite cause for carcinoma of the bronchus. Heredity has often been mentioned." page 606, (4364) omitted by Harris. Also, note that twelve of 28 patients had no information on smoking habits.

(4425) Clagett & Brindley; Chicago, IL; G555

"The opinion frequently has been expressed that the increase in bronchogenic carcinoma may be due to the increase in smoking and the inhalation of smoke. Nicotine, pyridine bases, phenol bases, ammonia and certain added hygroscopic agents all have been shown to act as irritants to the bronchial mucosa. Pulmonary carcinoma has been produced in experimental animals by the tar from cigarette smoke. Ochsner and DeBakey concluded: 'It is our definite conviction that the increase in the incidence of pulmonary carcinoma is due largely to the increase in smoking, particularly cigarette smoking, which is universally associated with inhalation.'" page 840, (4425)

(4440) Grace; New York, NY; G205

"Using the numerous investigations (by Roffo and others) reported in the preceding pages as a springboard

from which to make further conjectures on the relationship between tobacco poisoning and certain clinical entities which are generally associated with a heavy smoking habit, we may differentiate two such groups: 1. cancer of the lip and oral cavity, and 2. cancer of the lung. The former is most frequently encountered in pipe and cigar smokers who rarely inhale, but in whom the irritating substance of tobacco is deposited on the lips and tongue. In cancer of the lung, often occurring in cigarette smokers, this toxic irritant is deposited in the bronchi during the process of inhaling smoke. There appears to be no doubt whatsoever that, in the heavy smoker, tar, with its chemical byproducts, enters the etiological picture in the development of neoplasms." page 328, Harris' selected quotation of (4440)

(4477) Tinney; Rochester, MN; G500

"Unfortunately, bronchiogenic carcinoma does not have characteristic symptoms. The symptoms are the same as those produced by any pulmonary inflammatory disease and depend essentially on the size and location of the tumor. Cough was an early symptom in 81 per cent of the cases in this series. **The cough was usually dry and nonproductive at onset and did not differ from the so-called cigarette cough, that is so indigenous in the general population.** The cough does not become productive of a purulent sputum until the size of the tumor is sufficient to obstruct the bronchial lumen and cause retention of secretions in the distal bronchi. When the retained secretions become secondarily infected, attacks of chills and fever develop that are usually relieved in a few days by drainage of the secretions. Such episodes occurred in approximately half of the cases which I studied and the diagnosis of pneumonia was frequently made." page 355, (4477)

(4533) Holinger, Hara & Hirsch; Chicago, IL; G555

"The inhalation of tobacco in smoking is considered by some as a factor causing cancer. It is generally known that cancer among smokers is much more prevalent in the so-called smoke tract - the lips, mouth, larynx and bronchi - than in nonsmokers. Ninety per cent of a large series of patients observed at the Cook County Hospital were smokers. Fifty of our own patients were heavy smokers. **However, 14 stated that they did not smoke, and there is no mention of this habit in the remainder of the histories."** page 7, (4533)

(4554) Muller & Miller; Philadelphia, PA; G566

"Inhalation of light oil derivatives of coal tar and dusts containing silica have likewise been shown to be of etiologic significance in lung cancer. The high incidence of lung cancer in the male sex as compared to that of the female sex has been attributed to the use of nicotine, **but the recent increase in female smokers has not led to an increase in lung cancer in females.**" page 42, (4554)

(4560) Potter & Tully; Boston, MA; K500

"43 male lung cancer clinic patients, aged over 40 years, compared to 1,847 male clinic patients with diagnoses other than cancer. 30.2% heavy smokers and 7.0% nonsmokers among lung cancer cases. 23.0% heavy smokers and 26.0% nonsmokers among controls." (Harris' paraphrased results; figures do not appear in the cited article)

"Information on the use of tobacco was obtained from 2,927 male clinic patients over the age of 40. They were divided into those who used no tobacco, those who reported slight use, moderate use, and excessive use. Attack rates were computed for cancer of the buccal cavity, digestive tract, respiratory tract, skin, and for cancer of all other sites. There was a definite association between cancer of the buccal cavity and the use of tobacco. There also appeared to be some association between the use of tobacco and cancer of the respiratory tract. These findings confirm the opinion held by many clinicians." page 488, (4560)

(4615) Clerf & Herbut; Philadelphia, PA; G455

"Many writers believe that inhalation of tobacco smoke is a responsible factor. Since chronic irritation is generally accepted as a predisposing cause, there should be ample evidence to support the theory that inhalation of tobacco smoke, particularly from cigarettes, is a factor. This habit is practically universal and a majority of patients with carcinoma of the bronchus smoke either moderately or excessively. Irrespective of its being an etiological factor, **smoking more than anything else contributes to delay in diagnosis by making a common, early and important symptom, namely, cough.**" page 169, (4615)

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(4635) Horn; Baltimore, MD; G466

"The use of tobacco and its relation to lung cancer has been a favorite subject of investigation. Ochsner strongly affirms that the rise in bronchogenic carcinoma is caused by the increasing use of tobacco. Campbell in a statistical study found those engaged in the preparation and sale of tobacco to have an abnormal liability to lung cancer. Grace suggested that 'possibly the carcinogenic irritants from tobacco tar are deposited in the lung and the end result of this irritation in a biologically susceptible individual is the production of bronchogenic carcinoma.' **No one proposes an explanation, however, to interpret the fact that while by far the greatest increase in smokers during the past two decades has been among women, bronchogenic carcinoma has been seen strikingly more often in males than females.** In the University of Maryland Hospital series, forty cases occurred in men and five cases in women." pages 170-171, (4635).

Note: There is no information on smoking habits of 45 reported cases, in spite of author's awareness of the literature.

(4718) Berg, Poppe & Havlicek; Portland, OR; G555

"Since the question of use of tobacco appears on the routine history form at the Veterans Hospital, an unusually good record of this was obtained. In the entire series there were only four nonsmokers, and many of the patients were noted to be heavy smokers. The question of the relationship of cigarette smoking to the etiology of bronchogenic carcinoma has been an interesting one and has been discussed by many authors. **Since approximately 90 per cent of male patients smoke, no conclusions can be drawn from this fact alone."** page 452, (4718)

(4754) Humphreys; New York, NY; G500

"The outlook for a patient who develops carcinoma of the lung is so miserable that many doctors consider it completely hopeless. Because until recently primary carcinoma has been thought to be a rare disease, the possibility of its presence is too often overlooked by the general practitioner. Only after a protracted period of waiting for a turn for the better which fails to occur is he forced to realize that he is dealing with something more than an inflammatory process. Too often, even when the possibility is considered, there is

a tendency to procrastinate, in the conviction that, if a tumor is present, the patient is in any case doomed. This tendency is increased by the fact that these lesions frequently occur in heavy smokers whose early symptoms are masked by a long history of cough, and whose illness apparently begins with symptoms of acute infection, symptoms which respond deceptively well to sulfonamide or penicillin treatment. The discomfort of bronchoscopy is a small thing to ask of a patient who is faced with possibility of death from this disease, yet it is surprising how often the chance it affords of establishing the diagnosis early is withheld." page 3330, (4754)

(4819) Bradshaw; Winston-Salem, NC; G900

"Lung cancer occurs predominantly in patients over 40, but is occasionally seen in teen-age youngsters. For some unknown reason males are afflicted five or six times as frequently as females. This fact has been used by some as an argument that smoking has an irritating effect which is a factor in the production of lung cancer. Such reasoning has no foundation on either experimental or clinical evidence. The incidence of cancer in patients with truly irritating diseases of the bronchial tube, such as bronchiectasis, has never been shown to be greater than in normal individuals. Many patients, both male and female, who have lung cancers have never smoked." page 187, (4819)

(4822) Churchill; Boston, MA; G905

"Nothing is known about the cause of the disease that can be translated into effective preventive measures. It is possible that an actual increase in the incidence of pulmonary cancer has taken place during the first half of this century. Several statistical studies support such an interpretation. On the other hand, Boyd, who is in a position to speak freely of the shortcomings of pathologists, thinks the disease was not recognized twenty years ago because it was not looked for. At any rate, evidence that pulmonary cancer was on the increase led to several speculations about causative agents, and among other things, cigarette smoking was incriminated. Further knowledge about the nature and the mode of action of carcinogenic agents, and a careful recording of the smoking habits of ample number of patients with the disease, provide no factual evidence on which advice to give up smoking for this reason can be based. Exposure to radioactive ores has

been correlated with a high incidence of the disease in classical studies on European mine workers. It may be well to bear this in mind." page 456, (4822)

(4847) Levitt; Detroit, MI; G566

"Many investigators have endeavored to establish a connection between bronchogenic carcinoma and chronic irritation of the respiratory tract. Tobacco smoke, air pollution from the exhaust of automobiles, dust raised from tarry roads, have all been suggested as possible causes, but as yet, none of these factors has proven to be the specific cause." page 396, (4847)

(4858) Madore; Montreal, CAN; G655

"Opinions vary greatly on this point. The high incidence of cancer in males as compared with females has been attributed to the use of nicotine, but the recent increase in female smokers has not led to an increase in lung cancer in females." page 146, (4858) from Alwens & Jones, 1936, ref. 5.

(4859) Martin; New York, NY; Z600

"The pre-existence of chronic local irritation which may so often be shown to play a part in the causation of malignant growths of the oral cavity is not readily demonstrated in cancer of the larynx. Although excessive smoking with inhaling, voice strain and syphilis are undoubtedly etiologic factors in an occasional case, these forms of irritation cannot be shown to have a significant etiologic role in most cases of laryngeal cancer. The disease usually appears to arise spontaneously. Leukoplakia of the larynx (pachydermia larynges) sometimes undergoes malignant transformation." page 1366, (4859)

(4876) Quick & Brindley; Galveston, TX; G455

"Speculation concerning predisposing causes has been rife. Street dust, stone dust, exhaust from automobile fumes, and tobacco smoke have all been blamed. It is of interest that the curve of incidence of bronchiogenic carcinoma parallels the rising curve of cigarette sales. We should watch the incidence of carcinoma of the lung in women in view of the recent general trends in smoking." page 627, (4876)

(4866) O'Keefe; Philadelphia, PA; G566

> "Holinger and his associates reviewed the secondary etiologic factors in a recent paper. In their analysis of such inhalation irritants as coal dust, silica, exhaust gases, road tar and tobacco smoke, they concluded that **'without further corroborative evidence, (these) too, must be considered coincidental.'** Clerf and Herbut placed a unique and pertinent interpretation on the relationship of tobacco smoke: 'Irrespective of its being an etiological factor, smoking, more than anything else, contributes to delay in diagnosis by masking a common, early and important symptom: namely, cough.'" pages 347-348, (4866). Note: There was no information on the smoking habits of 131 patients reported in the article even though O'Keefe was aware of literature implicating cigarette smoking.

(4938) Hayes; Saranac Lake, NY; G555

> "These are unknown, although excessive smoking of tobacco and, in certain industries, radioactive emanations have been blamed. **The increase incidence has been parallel in the last four decades to industrial development with its noxious chemicals and gases."** page 895, (4938)

Incidence of cigarette smoking. It was the opinion of most American clinicians cited above that cigarette smoking incidence among lung cancer patients was not higher than that in the general population. Among 35 articles, there were four that favored causal hypothesis of cigarette smoking (4334) (4364) (4440) (4560). Each one was cited by Harris in his Table 2. Two other articles were used by Harris in his SOA Report (4156) (4759), but the remaining 28 were overlooked. The follow-ing overlooked articles contained a review of the literature implicating smoking as a cause of lung cancer: yet smoking habits of patients reported by the author were not mentioned (4046) (4718) (4866).

Smoking Habits Among Europeans

The earliest articles suggesting a causal relationship between lung cancer and cigarette smoking appeared in German medical journals and were later followed in English. It was probably more than a coincidence that early literature on cigarette smoking and lung cancer was published in German. There was a suggestion that Nazi medicine was against the use of tobacco that was manufactured and sold by Jews. An anti-tobacco organization flourished during the war.

Germany and Austria. The first suggestion of a causal link was made in 1929 by Lickint, based on a coincidental rise in incidence of lung cancer and in cigarette smokers. The first reported comparison of smoking prevalence in lung cancer patients and controls was reported in 1939 by Muller. During World War II, Schairer & Schoeniger confirmed Muller's conclusions that smoking prevalence was more frequent among lung cancer patients compared to a group of control among males in Germany. For completeness of this review devoted to the 1940's, the following publications in German since 1929 are included (see also Chapter III, page 218).

(2931) Lickint

> "Review of laboratory and clinical evidence on tobacco and cancer. Rise in cigarette use linked to rise in lung cancer." (quoted by Harris)

(3031) Mertens

> "Increased incidence of lung cancer linked to tobacco. Shift in cancer from oral sites to lower

respiratory tract linked to shift from pipes and cigars to inhaled cigarettes." (quoted by Harris)

(3572) Lickint

(Not quoted by Harris; needs English translation)

(3985) Muller

"Comparison of 86 male lung cancer decedents with 86 healthy men of the same age. 65.1% heavy smokers and 3.5% nonsmokers among the lung cancer cases. 36.0% heavy smokers and 16.3% nonsmokers among the control cases." (quoted by Harris; Muller discussed role of occupation; no further publications by Muller)

(4311) Schairer & Schoeniger

"Comparison of 93 male lung cancer decedents autopsied (average 53.9 years) with 270 men aged 53 and 54. 31.2% heavy smokers and 3.2% nonsmokers among lung cancer cases. 9.3% heavy smokers and 15.9% nonsmokers among controls." (quoted by Harris; no further publications after appearance of (4311))

(4893) Wassinck

"134 male clinic patients with lung cancer compared to 100 normal men of same age groups as cases. 54.8% heavy smokers and 4.8% nonsmokers in lung cancer group. 19.2% heavy smokers and 19.2% nonsmokers in the control group." (quoted by Harris; patients were from Amsterdam)

I am in the midst of collecting articles by each of the six German authors listed above. A recent trip to East Germany failed in finding additional information on the *Scientific Institute for Research on the Danger of Tobacco*, and the *Institute of Pathology, Friedrich Schiller University* in Jena. These were the affiliations of Schairer & Schoeniger when they submitted the results of a retrospective study of lung cancer patients and control subjects (4311). There were no subsequent

publications by Mertens, Muller, Schairer & Schoeniger and Wassinck during the late 1940's and 1950's. Only Lickint continued to publish on smoking and health through the 1950's and 1960's (See Chapter V). Muller wrote his comparative study of lung cancer patients with controls without lung cancer as a thesis and did not publish on any other medical topics.

Great Britain and Switzerland. The Science Citation Index affords an opportunity to determine whether the suggestions by German writers were accepted or denied by other Europeans. Until the analysis of citations is complete, there are a few articles compiled from Index Medicus:

(4267) Wegelin; Berne, SWI; G555

> "The effect of smoking may be similar now that Schurch and Winterstein, as well as Roffo have induced skin cancer by the use of tobacco tar. Some authors, such as Lickint, Arkin and Wagner, Fleckseder, Schrek, Thys and F. H. Muller emphasized the harmfulness of smoking, particularly the inhalation of cigarette smoke, and Muller found 56 heavy to extremely heavy smokers and only three nonsmokers among 86 men with lung cancer. The remarkable preference for the male sex is accounted for by this factor, but it must be noted that despite the increase in smoking among women, there is not yet any shift in the sex ratio. Although Mertens obtained epithelial metaplasia of the trachea and bronchi and degeneration of the mucosa with purulence in mice exposed for a long time to the inhalation of tobacco smoke, he did not obtain lung cancer, and the etiologic relevance of smoking to the induction of lung cancer is not yet established." page 38 of English translation, (4267)

(4336) Harnett; London, GBR; G506

> "The percentage of smokers was estimated in a group of 69 men and 18 women, mostly from one hospital. Of the men 4.3 per cent. were non-smokers, 26.1 per cent. moderate, and 40.5 per cent. excessive smokers (over 3

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oz. of tobacco per week) with 29 per cent. not stated. **Of the women, one-third were non-smokers,** one-third not stated, and the remaining third were moderate smokers." page 36, (4336)

(4933) Fulton; London, GBR; G460

"No attempt has been made in this group to analyze the cases in terms of the possible effect of tobacco. **Case histories, unless designed in such a way as to cover this point in specific terms, do not provide information of sufficient accuracy and consistency to use as a basis for analysis.** It would not be surprising to find that tobacco was an etiological factor and, despite the fact that smoking is by no means confined to the male sex, it may have some bearing on the differing sex incidence. It may, for example, be important to determine whether the subject habitually inhales cigarette smoke, or whether it is merely puffed in the mouth. My impression is that most women smokers do not habitually inhale, while most men do.

The possible relationship between tobacco and carcinoma of the lung is being specially investigated by Dr. A. Thelwall Jones in Liverpool, and while the results of his investigation have not so far proved conclusive, the evidence to date points to tobacco as an etiological factor of possible statistical significance." page 778, (4933)

(4950) Mason; Newcastle-upon-Tyne, GBR; G650

"Perry of the London Hospital, has found that industrial exposure to arsenic and certain other metallic substances may probably be associated with the aetiology of lung cancer; but such industries are not, so far as I know, represented in our area. Perry has also remarked that arsenic is present in carcinogenetically significant quantities in cigarettes; but this **is difficult to reconcile with the disproportionate sex-incidence despite the vast increase of smoking among women,** especially since married women appear to be more commonly affected than their single sisters." page 587, (4950)

The above list will be expanded after completion of searching the Science Citation Cumulative Index for 1945-1954 (see Chapter V).

Questionable Applicability of German Studies to Americans

The most important reason in questioning the applicability of German studies to the United States is that the incidence of smoking habit among Germans did not necessarily apply to Americans during the 1940's. In a 1935 Fortune magazine poll, the incidence of smoking was 53% of adult men and 18% of adult women (3541). The survey noted that incidence of smoking for men and women was higher among urban populations.

During 1939 and 1940, Ley and his collaborators questioned life insurance extension examinees regarding their smoking and drinking habits. The responses were confidential so that the examinees had no reason to withhold information with respect to their habits. The conclusions relating to smoking habits are in a highlight publication written by Short, Johnson & Ley from the Life Extension Examiners, New York (3982).

> "In an attempt to learn what, if any, symptoms are produced in comparatively healthy ambulatory individuals by the use of tobacco, an unselected group of insurance policy holders were asked to fill out a questionnaire at the time of their periodic health examination. The questionnaire was designed to elicit their practices with reference to the use of tobacco, but contained no reference to physical signs or symptoms. This latter information was obtained independently from the physical examination and medical history which were recorded separately. Thus, by separating the time and method of obtaining the two kinds of information, it was hoped to avoid suggestion and bias. **Of 2,031 cases studied, 1,292, or 63.7 per cent, habitually used tobacco; 496, or 24.4 per cent, were nonusers; 104, or 5.1 per cent, used it only occasionally; and 139, or 6.8 per cent were former users who had discontinued the practice.** ... The complaints recorded are of especial significance because they were entirely spontaneous, written by the examinee

on a history form, and not elicited by questioning. It should be emphasized that both groups were treated exactly alike and the findings therefore cannot be biased. We believe that the findings in this study indicate a trend in accordance with the recent report of Pearl, who found mortality markedly increased among heavy smokers. It is hoped that further studies will demonstrate more definitely the manner in which tobacco exerts its influence and the chief hazards attached to its usage." pages 587-589, **(3982)**

In 1940 Ley reported the incidence of smoking and drinking among examinees for life insurance extension (4099). The responses were confidential so that the examinees had no reason to withhold information with respect to their habits. The conclusions derived from 10,000 examinees were as follows:

"The incidence of both smoking and drinking among males is fairly constant after the age group 20-29. In all age groups the male incidence for smoking is higher than for drinking. The frequency of both smoking and drinking among females reaches a peak in the decade 20-29 after which point both practices decline through life. Unlike the experience for males, the female incidence of drinking is higher at every age period than that of smoking, with a slight exception for the youngest age group.

The practice of smoking among males is higher in the New York metropolitan area than in the rest of the country up to the age group 40-49. After that point the New York incidence is lower. The habit of drinking among females is higher at each age group for those in the New York area.

Approximately 64 per cent of males and 21 per cent of females over 10 years of age in the United States use tobacco. Approximately 57 per cent of males and 29 per cent of females use alcohol. Approximately 7 per cent more men smoke than drink, yet 8 per cent more women drink than smoke. **Of the total figures, regardless of sex, approximately 43 per cent of the population use tobacco and 44 per cent use alcohol."** page 63, (4099)

The geographic distribution of examinees was not mentioned by Ley, other than differentiating the New York metropolitan area

from the rest of the country. There was no discussion of health differences associated with smoking and drinking.

A questionnaire sent by Schwartz (4568) to about 50 sanatorium directors contained the following questions:

> "1. Do you think smoking is harmful to tuberculosis patients?
> 2. Do you discourage your patients from smoking?
> 3. What rules, if any, do you set up toward control of smoking?
> 4. What arguments do you employ to discourage the habit among your patients?

The responses were summarized by Schwartz from Pine Crest Sanatorium, New York, as follows:

> "A questionnaire was sent to about fifty sanatorium directors to obtain their opinion concerning smoking. Only 2 per cent felt that it was not harmful, but only 16 per cent had rules which rigidly forbade the practice. Most of the men permitted smoking in certain cases or ignored the fact that the rules were being broken. This attitude is engendered by the fact that it is quite difficult to discourage patients from a habit of long standing in return for a benefit which is of questionable value. An examination of the more recent literature leads to the conclusion that since smoking is harmful even to normal people it is bound to have a deleterious effect upon the respiratory tract of individuals who are suffering from tuberculosis. It is felt that the best approach to the problem would be a definite rule forbidding smoking with frequent explanations about the dangers inherent in the practice." page 1542, (4568)

Schwartz used 22 references in his discussion of health effects of smoking. There was no mention of any German author; Roffo was mentioned as quoted by an American author. The following references appeared in Schwartz's list of references, as well as in Harris' SOA report: Bogen, Hoffman, and Proetz. However, it should be noted that the question was specific for tubercular

patients. The responses among the directors were as follows: 72% that smoking was harmful in excess; 2%, not harmful; 26% definitely harmful.

Macklin wrote three articles criticizing the literature on increase in lung cancer which she interpreted as unproven during the 1940's. The articles (4059) (4244) (4857) are highly recommended for detailed reading because pitfalls in dealing with cancer statistics could be applied to publications not only for the 1940's but also through 1966 (Part Three). Macklin's most important conclusions were items 5 to 8 as follows"

> "5. The question we wish to determine is not whether lung cancer, meaning by that diagnosed lung cancer, is increasing in hospital cases, but is diagnosed lung cancer increasing in the population of the age and sex distribution which is capable of showing it? Therefore, the only way of determining this point is to study the incidence of diagnosed lung cancer in the population at large, and not in the small fragment of the population which comes to autopsy. Therefore, data from all hospitals within a state for two periods chosen so that the age and sex distribution of the population of the state is known, thus preferably in a census year, should be added together and analyzed. Cities are not large enough in their scope, since they draw obscure cases from surrounding rural areas in different proportions in various years. Each state, however, has usually centers that are apt to draw patients from within their own borders.
>
> 6. It will probably be found that diagnosed lung cancer is increasing both relatively and absolutely, but the increase will probably be much smaller by this method than by the ones adopted by most workers, in which age and sex distribution of the lung cancer cases and of the standard group were ignored. Lung cancer will be increasing because it is being diagnosed in more cases in which it exists than was formerly the case, and will be increasing no doubt because persons of lung cancer age are having fewer diseases to die of today than they had before, and hence must die in ever increasing numbers of the ones which remain.

7. The data which are used to support the idea that lung cancer has increased faster than other forms of cancer cannot be used to support that conclusion, since we do not know what proportion of lung cancer cases were unrecognized formerly and what proportion are unidentified today. We can merely state that diagnosed lung cancer is increasing at a rate which appears to be faster than that of other diagnosed cancers.

8. The search for environmental factors supposed to be the basis of the unduly great increase in lung cancer should await further proof that the increase in diagnosed cases has been as spectacular as it has been claimed to be." page 324, (4857)

Experimental Carcinogenesis

The animal studies reported during the 1940's were mostly reported by Roffo on "tobacco tar" applied to rabbit ear. I have obtained additional references by Schurch, who reported results contrary to those reported by Roffo in the 1930's (See also page 243 and (3570) (3571) (3987). The skin painting studies in mice and rats were either negative or showed less activity compared to topical effects of coal tar. There were two mouse inhalation studies that were negative in results.

Roffo's rabbit experiment and other studies. The experiments on "tobacco tar" conducted by Roffo during the 1930's were extended through the 1940's (see Chapter III, pages 236-244). The contents of articles that were omitted in Chapter III, 1930's, and those published during the 1940's, can be summarized as follows:

(a) Oral leukoplakia (3035) and gastric cancer (3126) (4112) (4211) (4214);

(b) Carcinogenic effects on rabbit ear from repeated administration of tobacco tar (4011) (4012) (4013) (4014) (4018) (4111) (4113) (4116) (4212) (4213) (4312) (4313) (4315) (4316);

(c) Detection of benzopyrene in tobacco tar by spectrometer and fluorescence (3942) (3948) (4017);

(d) Carbon monoxide in blood of cigarette smokers and potential cardiovascular effects, co-authored with Roffo, Jr. (3247) (3883) (4016) (4114);

(e) Exchange of correspondence between Roffo and Florey from Chicago (4275) (4276) and publication of Florey's article in Spanish (4274);

(f) Distribution of anti-smoking leaflets and publication of anti-smoking activities in 1942 issues of Boletin del Instituto de Medicina Experimental (4276) ; and

(g) High incidence of oral and lung cancer among cigarette smokers (4215) (4314) (4317) (4333).

Latin American and North American reaction to Roffo's publications. The scientific validity of Roffo's rabbit experiments were criticized because of manner of extraction of "tobacco tar." An excessively high temperature was used characterized as a process of "destructive distillation." Jaffe, Jaffe & Potenza, from Caracas, Venezuela, expressed this criticism in a Spanish article that needs translation. Their brief four-paged report (4640) was a theoretical criticism based on rat experiments and was overshadowed by over a thousand pages of Roffo's results on

"tobacco tar" in rabbit experiments. Two Latin American publications acknowledged the reports of Roffo without offering any confirmation (4203) (4467), but other Latin Americans appeared to have ignored his publications (4034) (4074) (4320) (4521).

Roffo's scientific publications were included in an anti-smoking article entitled *Universal Toxicomania of Tobacco* (4115). The posters are English translations of Roffo's Spanish anti-smoking leaflets distributed in his Institute's "Boletino" (4276). In 1943, several authorities from Europe contributed to a *Libro de Oro* which included Hartmann (4048), Wassink (4893), and others that will be ascertained as soon as I obtain a copy from Buenos Aires.

Conflicting results among Roffo, Flory and Sugiura in rabbit experiments. Roffo reenforced his rabbit ear painting experiments by injecting tobacco tar directly into the lung parenchyma (see Chapter III, page 238). Roffo published a summary in English:

> "This process is characterized by the production of 4 little tumours in the left lung lobe (site of injection), presenting all of them the structure of squamous carcinomata with horny globules. I consider this result as a contribution of value to the explanation of the abundant lung cancerization in men. Although it could be reasonably objected that the repeated injection of a drop of tobacco tar does not correspond with what is going on in ordinary human life and that such a brutal action is bound to produce a trauma, we nevertheless wanted to point out, once more, the carcinogenic function of this product, either injected in the lung, or in other tissues. As for discarding the objection of the energetic action of the injection which might be considered as a coadjuvant cause in the development of this process, we but need to remind the cancerization

obtained by us in rabbits, by a superficial painting of their ears' skin with tar, each 2-3 days, without any other factor interfering." page 115, (4313)

Flory, a pathologist from the University of Chicago, repeated Roffo's ear painting experiments with the following results:

"Twelve rabbits were painted on the ears with a tar produced by the destructive distillation of tobacco at from 350-700°C. Between the 49th and 79th day all rabbits developed tumors at the painting site. The rabbits lived from 238 to over 600 days. Sixty-eight of the tumors examined histologically were papillomas, and 5 were carcinomatoid tumors. No carcinomas were produced. A 130-150°C. destructive distillate tar produced tumors in 16 out of 17 rabbits, but more slowly than the 350-700°C. tar. Forty of these tumors were papillomas and 5 carcinomatoid tumors.

Twenty-four rabbits were painted with tar obtained by smoking tobacco in pipes. Tumors were produced in from 37 to 374 days in 22 out of the 24 rabbits. Seven animals have lived over 640 days. Thirty-six tumors examined histologically were papillomas and 2 were carcinomatoid tumors. No carcinomas were produced.

What then is the status of these carcinomatoid tumors? In this work with tobacco tars evidence does not indicate what the ultimate fate of these tumors would have been. Most of the tumors were identified only at autopsy, although some were seen very early in the painting period. It is of importance to note the absence of definite metastases in all 11 animals with carcinomatoid tumors. It was not proved that such tumors could produce distant metastases. In view of the work of Rous and Kidd it would seem likely that the invasive behavior of these tumors depended on the repeated application of an extrinsic stimulus rather than on an intrinsic capacity for unrestricted growth. There is no evidence that the production of these carcinomatoid tumors in rabbits is an indication of carcinogenic activity of the tobacco tars." page 274, (4037)

Although Flory specifically denied carcinogenic activity, Roffo interpreted the negative result in the opposite way (4276), as did Harris in his SOA report.

Sugiura from the Memorial Hospital, New York City, painted rabbit ears with combustion products of tobacco distilled between 100 to 900°C. **(4091)**. Sugiura's article is a **highlight publication** with results that conflicted with those of Roffo:

> "Our results with rabbits are not in conformity with the findings of Roffo, who succeeded in producing a large number of papillomas and true malignant growths after continued application of tobacco tar. Since Roffo's results seem undoubtedly significant, it is possible that some other factor than tobacco is responsible for the discrepancy. Roffo subjected tobacco of various kinds to fractional combustion distillation in a stainless steel retort, whereas we used an iron retort. It is difficult to believe that any hydrocarbons with a phenanthrene nucleus, which Roffo claims are contained in his combustion products of tobacco, should break up by our method of distillation. In addition, Kennaway has shown that the carcinogenic substance of coal tar is not found in any appreciable quantity below 550°C.
>
> Little information is available concerning the presence in tobacco tar of carcinogenic hydrocarbons identical with those contained in coal tar. In 1932, Cooper, Lamb, Sanders and Hirst subjected tobacco tar products to spectrographic analysis to disclose a possible carcinogenic agent but reported inconclusive results. It was said, however, that all the samples of tar, whether obtained at low or high temperature, exhibited fluorescence. Schurch and Winterstein, in 1935, reported that the fractions obtained from tobacco tar did not contain polycyclic aromatic hydrocarbons related to the carcinogenic hydrocarbons contained in coal tar. Recently Roffo made intensive spectrographic examinations of products of combustion of tobacco and found hydrocarbons with a phenanthrene nucleus identical with that in the carcinogenic hydrocarbons present in coal tar. Roffo, however, made all his spectrographic analyses with impure complex mixtures. No definite conclusions can be drawn from the absorption bands of these bodies until the specific hydrocarbon is isolated in pure chemical form." page 48, **(4091)**

The subject of analysis for polycyclic aromatic amines is discussed below (*Occupational Exposure to Coal Tar*).

Suguira's negative results in rat ear. Sugiura noted that although rat skin was extremely resistant to the carcinogenic action of coal tar and hydrocarbons, it was highly susceptible to the cancer-producing effects of ultraviolet rays (4091). Suguira cited Roffo and Beard who obtained positive results derived from rat ear painting experiments. However, Suguira obtained negative results using tobacco tar:

> "A series of experiments was conducted to determine whether the ears of rats share the exemption from the carcinogenic action of tobacco tar that is shown by the skin of mice. The internal surface of the ears was painted with the combined dark brown oily liquids of the first and second distillates, distilling at 300-900°C., two to three times weekly for 48 to 65 weeks. Thirty of 35 rats survived the long-continued tar paintings but showed no evidence of tumors." page 46, (4091)

Conflicting results in mouse skin painting experiments. The positive results obtained with tobacco tar skin painting rabbit studies during the 1930's could not be duplicated in mice during the 1930's (3230). An English translation of Taki's presentation during a meeting of the Japanese Society of Pathologists has been obtained:

> "Clinically it has been well-known that in smokers there is a high incidence of cancer of the oral cavity, including lip and tongue cancers. Many studies have been conducted to determine whether the cause is mechanical or thermal irritation at the time of smoking, chemical action of tobacco fume or tobacco tar, or a combination of both. In all of these studies on experimental animals, death was induced early through the action of nicotine and other toxic materials contained in tobacco tar, and it has been difficult to demonstrate carcinogenicity of these factors. Some investigators have therefore used nicotine alone or tar from which nicotine has been removed, but these agents have been weakly carcinogenic, and many workers have applied other

irritants, or have administered hyolesterin or coal tar to increase carcinogenicity. Although there have been a few reports on successful carcinogenesis, they have all been as result of combining other substances. In the mouse, there has not been an instance of success using tobacco tar from which nicotine and other alkaloids have been removed.

We collected tobacco tar and dissolved it in ether, shook the solution with addition of 1% hydrochloric acid to remove nicotine and other alkaloids, washed the preparation with water and dehydrated it with anhydrous sodium sulfate, and removed the ether. This tobacco tar preparation was painted onto the dorsal skin of mice every other day.

In 12 mice that survived for 100 days, one developed an epidermoid tumor and 2 developed papilloma. The animal which developed the epidermoid tumor formed a papillary tumor on about the 60th day which grew to a size of about 1/3 cm. This dropped off, but growth resumed, becoming rapid about the 40th day, to form what appeared grossly to be an epidermoid tumor by the 167th day.

The two cases of papilloma have retained their morphology. One developed around the 40th day and is continuing to grow. We are maintaining these animals to see whether metastasis may occur and to conduct transplantation experiments. Studies are also under way to see whether a tumor may be induced by oral administration of agents in the rat. Although the incidence was low, we succeeded in demonstrating that carcinogen(s) could be shown to be present in material obtained from coal tar." page One, English translation of (3737)

Suguira attempted to replicate Taki's results without success:

"Painting the skin of C57 black mice and dba mice, as well as the ears of rats of Wistar Institute stock and of rabbits of common stock, with tobacco tar failed to produce any cancerous change. The proliferating capacity of mouse sarcoma 180 and the Flexner-Jobling rat carcinoma was unaffected by tobacco tar or pure nicotine solution when the solutions were adjusted to pH 7.4. Another factor which might account for the disagreement between our findings and those of Roffo and Taki is the use of animals of different strains. It is now known that animals of various strains possess marked differences in susceptibility to the carcinogenic action of hydrocarbons. From the fact that only squamous

carcinoma has been obtained in the course of subjecting a large number of mice to the action of tobacco tar, compared with the very high incidence of cancer in mice treated with coal tar, it seems reasonable to classify **tobacco tar as a weak carcinogenic agent."** pages 48-49, **(4091)**

Flory compared the results of tobacco tar with those of coal tar:

"Although the stock mice used in these experiments readily developed squamous cell carcinomas of the skin when painted with coal tar of known carcinogenicity, only 2 squamous cell carcinomas developed as the result of painting animals of the same stock with tobacco tars. Both tumors arose at the sites of painting. One developed after painting with the denicotinized 350-700°C. destructive distillate tar for 8.5 months, the other after 17 months' application of denicotinized pipe tar. Since no similar spontaneous tumors had been seen in some 2,000 of these mice, the production of these squamous cell carcinomas indicated that both tars had a low but definite carcinogenic activity. The earlier time of cancerization, as well as the greater capacity to produce papillomas, indicated that the activity of the 350-700°C. destructive distillate was greater than that of pipe tar. Both tobacco tars were a great deal less active than the potent coal tar used in the control experiments. These observations are in accordance with those of Cooper, Lamb, and Sanders, Campbell, and Siguira, but the work of Taki indicated a higher carcinogenic activity of pipe tar on mice." page 274, (4138)

The above comments were the origin of reference to tobacco tar as less active in potency than coal tar.

<u>Mouse inhalation studies.</u> Lorenz, Stewart, Daniel and Nelson, from the National Cancer Institute, reported negative results in the one of two American publications on inhalation testing of cigarette smoke prior to 1950:

"An automatic tobacco smoking machine was used to expose mice for several hours daily to tobacco smoke. Ninety-seven experimental and 97 control mice (strain A)

of both sexes were kept in a chamber through which the smoke passed, for from 25 to 250 days. The maximum time was 693 hours. The average smoke content of the air in the chamber was 1mgm. per liter. Calculations gave the amount of tar deposited in the respiratory passages of any one mouse during the entire run as roughly 0.5 gm. No lung tumors were induced by the tobacco tar, for the average number of spontaneous pulmonary tumors was the same in the experimental as in the control animals. Pigmented foci were observed in the lungs of all mice exposed for more than 3 months, probably indicating areas of deposited tar. A few experimental animals showed inflammatory lesions of the stomach and duodenum. Further studies are now in progress." page 123, (4348).

Note: The above article by Lorenze et al and another on inhalation testing are **highlight publications.**

In a panel discussion during the 1949 National Cancer Conference, the proceedings contained paragraphs suggesting that there was a second American study prior to 1950::

"Experimental studies were reported in which strain A mice were exposed to the inhalation of tobacco smoke for four hours per day for twelve months. **No increase in the occurrence of lung tumors was noticed.** The tar from such smoke was painted on the skin and injected into the subcutaneous tissues and tar suspensions were injected intravenously and fed **without the appearance of tumors in the lung or any other organ** during the life span of the animal. It was pointed out that provided oxygen is present, polycyclic hydrocarbons of known carcinogenic activity are not formed on the combustion of tobacco. Oxygen is present in cigarette smoking. A clinical review of 200 case histories of patients with bronchogenic carcinoma was reported suggesting that tobacco smoking is a significant factor in the production of human lung cancer. Lack of time prevented further discussion of this problem." page 203, (4914)

I am attempting to find the laboratory or spokesman for the experimental studies described during the panel discussion.

Rat inhalation study. I have selected this article as a **highlight publication.** Haag, Weatherby, Fordham & Larson conducted daily life span exposure to cigarette smoke on rats.

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The exposure in a suitable chamber lasted every half-hour, 14 times daily, from weaning age, daily for the entire life span. Compared to cage controls and smoke controls, the smoke exposed rats had no necropsy lesions that were particularly characteristic. Blood pressure determinations taken at regular 2 month intervals showed no differences between the three groups. Weekly weight determinations showed that the cage controls attained and maintained greatest average weight, the smoked exposed groups somewhat less, and the values for the smoked controls being intermediate. The average life span of smoke exposed group was 642 days, smoke controls 544 days, and cage controls 631 days (4667). The exposure level was fixed. As a pioneer effort in inhalation toxicology, the protocol cannot be criticized because determination of maximum tolerated dose was not introduced until two decades later.

Irritant Effects of Tobacco Smoke

When this project was reassigned in October 1988, I was requested to avoid any discussion of Harris' statements attributed to cigarette manufacturers. Exhibits consisting of internal reports and correspondence introduced during Harris' deposition and trial proceedings were not available to me, although I read all references relating to his SOA Summary Statement 8, pages 32-27, entitled *Research on Smoking and*

Health Performed or Sponsored by Cigarette Manufacturers (3460) (3464) (3465) (3658) (3667) (3668) (3770) (3671) (4126) (4166) (4254) (4367) (4612).

Larsen, Haag & Silvette. I have selected the Tobacco Monograph as a **highlight publication** because of its excellent summary of the literature on *Irritant Effects of Tobacco Smoke*. Most methods for determining irritation of tobacco smoke were evaluated by the authors at their pharmacology laboratory, Medical College of Virginia. It is difficult to improve on their scholarly description of irritant effects of tobacco smoke. The text starts with the following paragraph:

> "The problem of measurement of tobacco-smoke irritation is a most difficult one. Obviously, biological manifestations of irritation must be used and quantitated as best possible. However, the various manifestations are not necessarily interdependent. In consequence, depending on the chemical nature of the irritant, one manifestation of irritation may be affected to a much greater extent than another. Since tobacco smoke is a very complex mixture of substances, which can be varied through changes in the composition of the tobacco smoked, it is apparent that no single biological manifestation of irritation can be used as a complete reliable criterion for evaluating its irritating potency. This does not mean that the various methods proposed for measuring irritation are of no value, but rather that the significance of each much be carefully interpreted and an over-all picture should not be drawn from results obtained by any one method." page 400, (6101)

The opening paragraph was followed by a description of over a dozen clinical and laboratory techniques for measuring mucosal irritation, a characterization of irritation by tobacco constituents, and the influence of hygroscopic agents on irritant

action. The concluding paragraph was as follows:

> "For several years during the 1930's, the controversy between the proponents of diethylene glycol, and those of glycerine, as a humectant for cigarettes was lively and, at times, acrimonious. The conclusions of Mulinos and Osborne and of Flinn as to the relative lack of irritation of diethylene glycol were approved by Clement, Greenwald, and Cone, Hatcher and Greenwald. M. A. Lesser criticized the latter authors for giving a one-sided picture of the value of diethylene glycol as a hygroscopic agent, and for failing to make mention of the adverse literature in this connection. Fishbein then challenged Lesser's qualifications to judge clinical evidence, and pointed out that Lesser in earlier writings had devoted himself largely to encouraging the use of glycerine. Temperately, Bogen briefly reviewed the glycerine-diethylene glycol controversy, and pointed out the necessity for more work. Later, Fabricant extensively reviewed the literature, and concluded: 'Preponderant investigative opinion indicates that there are no differences in the irritating properties of the two types of cigarettes.' The claims made for diethylene glycol have not been substantiated. The experimental evidence appearing since Fabricant's review have borne out his conclusions. Instead of Greenwald's belief that the degree of edema was not influenced by the blend of tobacco or the method of manufacturing the cigarettes, but was purely a function of the hygroscopic agent (and greater for glycerine than for diethylene glycol), the opinion now seems to prevail that neither glycerine nor diethylene glycol significantly alters the irritant properties of cigarette-smoke." page 407, **(6101)**

There were over sixty references cited by Larsen, Haag & Silvette, and 25 articles were used by Harris in his SOA report.

Justification for research on irritant action of tobacco smoke. My own interpretation of significance of research on irritant action of tobacco smoke is as follows: Since the turn of the century, the most conspicuous pharmacologic effect of tobacco smoke was mucosal irritation, specifically , of the conjunctiva, nose, mouth, pharynx, larynx, and tracheobronchial

passages. Irritation was not specific for tobacco smoke, but was induced by products of fuel combustion. What was unique for tobacco smoke was the presence of nicotine and this alkaloid was suspected of being the cause of irritation, cardiovascular disease, bronchopulmonary disease, and central nervous system effects.

Tobacco researcher from cigarette companies and medical schools were undoubtedly aware during the 1930's and 1940's that there were publications from Germany, Japan, Argentina, Great Britain and the United States that the majority of lung cancer patients were cigarette smokers. Researchers were also aware that the most widely accepted explanation for pulmonary carcinogeneses was bronchopulmonary irritation. Simon, Hueper and others, as early as 1928, grouped irritants to chemical, bacterial, mechanical, and irradiation. The most prudent approach was to determine ways of reducing irritant action of tobacco smoke. Prior to 1950, that tobacco smoke irritation was a cause of lung cancer was a hypothesis based on a dozen clinical studies, another dozen animal skin painting experiments, and accepted as a fact by two dozen authors. There were also about two dozen authors who were interested in the irritant action of cigarette smoke for the expressed purpose of reducing acute or short-term effects on the ophthalmic, nasal, oral, pharyngeal, laryngeal and broncho-pulmonary mucosa. Whether mucosal irritation also caused chronic diseases was open to question and was

not necessarily subscribed to by researchers from Virginia, New York, Illinois, Missouri and District of Columbia. The articles listed below were published during the 1930's and 1940's.

Publications from Virginia. Most publications cited by Harris on irritant action of cigarette smoke were either from Philip Morris or the Medical College of Virginia, both of Richmond, VA. The pertinent quotations I selected relate to the expressed purpose of conducting the research, i.e., to reduce acute irritant action of tobacco smoke.

(3559) Greenwald (Philip Morris & Co., Ltd.)

> "Due to the great increase in the use of cigarettes and their effects on the mucous membrane of the upper respiratory tract, the causes of irritation and methods for removing some of the irritant properties of smoke have been studied. A series of studies of the blend of tobacco, as well as its method of manufacture, finally pointed to a most surprising fact - that the main source of irritation from cigarette smoke was not the tobacco but the hygroscopic agent. The hygroscopic agent is a substance that is added to tobacco to maintain the moisture content during the course of manufacture. It also serves the important purpose of keeping the finished cigarettes 'fresh' until they reach the hands of the consumer. The hygroscopic agent commonly used is glycerine. It would not seem that glycerine, on first consideration, so generally known as a soothing agent, could have any harmful effects. In cigarettes, however, the glycerine burns with the tobacco - and burning glycerine forms, among other smoke products, a highly irritating and toxic substance. Some hygroscopic agent, of course, is necessary, but it would be preferable to use one which would have the necessary moisture-retaining properties but which on combustion would not produce such an irritant. Such a material, suggested for use as a hygroscopic agent, is **diethylene glycol. It has all the desirable properties of a hygroscopic agent but, because of its chemical constitution, cannot on combustion produce an irritant such as that produced by the burning of glycerine.** The theoretical advantages of diethylene glycol over glycerine were perfectly

apparent to the chemist. Before it was possible to be sure that the use of diethylene glycol in place of glycerine made an actual difference in the irritating properties of the smoke, it was necessary to study the smoke itself and its effects. These studies were conducted along pharmacological and clinical lines. ... Tests on rabbit's eyes and on man's nose, throat, mouth and lungs showed conclusively that the irritation caused by smoke from diethylene glycol-treated cigarettes is much less than that from glycerine-treated cigarettes." pages 467-468, (3559)

(3662) Greenwald (Philip Morris & Co., Ltd.)

"Not so long ago, in a summation of our knowledge, it was said that the slight deleterious effects of smoking were not sufficient to overbalance the pleasures to be derived therefrom, with reservations in certain instances of organic disturbance in which the use of tobacco is contraindicated. Numerous conflicting reports of the effects of smoking led to this statement. Whether or not smoking has adverse influences on the vascular system, the lungs, the digestive organs, or on pregnancy, fertility, or growth, or as a possible cause of cancer - are all moot questions. Unfortunately, the effects of smoking constitute a gap in our knowledge and with the exception of the effect of smoking on irritation of the upper respiratory tract, there is much room for study. With the great prevalence of cigarette smoking, there has been an increasing amount of irritation of the upper respiratory tract. Even the various cigarette manufacturers realize this by continuously stressing the mildness of their products (freedom from harsh irritants, throat ease, elimination of coughs, etc.). These improvements are effected by the proper choice of tobaccos and by various methods of treatment of the tobaccos, many of which are 'dark secrets.'" page 366, (3662)

(3772) Cone & Davis (Philip Morris & Co., Ltd.)

"It has been pointed out by Conde that the control of the moisture content of tobacco is one of the most important phases of manufacture. While some hygroscopicity data are available, they are insufficient for the types chiefly used in this country, and the writers had planned additional work to measure the equilibrium vapor pressure of various types, over a wide range of temperatures and moisture values. It was realized, however, that there is no such thing as an 'absolute'

moisture content for any sample of tobacco; the value obtained depends on the method used, and few laboratories agree on the same method. Methods include drying the samples in ovens, for varying times, at different temperatures, with or without forced air circulation; drying at room temperature over various desiccants, under atmospheric pressure or vacuum; various distillation procedures with solvents immiscible with water; and indirect procedures involving conductivity or dielectric constant. In this work an attempt has been made to compare six methods in common use." page 219, (3772)

(3776) Haag (Medical College of VA)

"When aqueous smoke solutions, obtained from diethylene glycol-treated and glycerin-treated cigarets, were instilled into the conjunctival sac of rabbits, no differences in the irritating properties of the two types of cigarets were observed as judged by the appearance of hyperemia, edema, blepharospasm, and the objection of the animal. Likewise, smoke solutions prepared from the two types of cigarets were found to have the same toxicity upon white mice by intraperitoneal injection." page 346, (3776)

(3777) Haag & Ambrose (Medical College of VA)

"In the rat both diethylene glycol and glycerin lead to an increase in urinary oxalic acid, although it appears that, quantitatively, glycerin is definitely less prone to do so. In the dog, diethylene glycol fed in the amounts reported herein provoked an insignificant increase in the urinary oxalic acid, much of the drug being eliminated unchanged in the urine." page 100, (3777)

(3872) Forbes & Haag (Medical College of VA)

"It would appear, then, that from 7-8 per cent of the total semisolid constituents of smoke consisted of unchanged hygroscopic agent when such material was present in the original cigarette, whether it was glycerol or diethylene glycol. Assuming that these substances were applied in amounts approximating 3 per cent, about 22 per cent of that contained in the tobacco smoked was transferred to the main smoke stream. A similar percentage recovery was obtained for nicotine in the main smoke stream. Results of experiments concerned with the further distribution of nicotine

during cigarette smoking suggest that most of the remainder of the hygroscopic agent passed into the side smoke stream or was deposited in the butt, as was found to be the case with nicotine. While an elaborate discussion of the toxicology and pharmacology of hygroscopic agents seems hardly within the scope of this paper, it may be noted that even in the case of diethylene glycol the amounts transmitted in the smoke of cigarets are far below those shown to be injurious by oral administration to experimental animals. In what manner the organism would respond to various concentrations of such an agent given by inhalation has never been reported." page 718, (3872)

(4042) Haag (Medical College of VA)

"Employing the blood pressure response as a biological test, it was found that the differences in nicotine content in several brands of cigarettes could be correlated with the effects of solutions prepared from their smoke. Likewise, the toxicity of these smoke solutions by intraperitoneal injection into mice war proportional to their nicotine content. It is concluded that the actions of cigarette smoke solutions, as regards their acute toxicities and their effects on blood pressure by intravenous injection, are due to their nicotine content." page 618, 4042)

(4527) Finnegan, Larson, Haag (Medical College of VA)

"It would seem clear from these results that with many individuals nicotine becomes a major factor in their cigarette habit. Equally certain, with many individuals nicotine is not a factor in their cigarette habit. Even in these individuals in whom nicotine has become a major factor we feel that a cigarette containing no nicotine would be grudgingly accepted as better than no cigarette at all. page 96, (4527)

(4666) Larson, Haag & Finnegan (Medical College of VA)

"We have previously shown both man and the dog that only about 10 per cent of administered nicotine is excreted unchanged in the urine. The fate of the remaining 90 per cent remains to be elucidated. Interpreting this in the light of our findings concerning the fate of nicotine in the animal body, it seems fair to assume that the nicotine metabolite that yields a red color with CNBr is a product of cleavage of the pyrolidine ring between the nitrogen and the 5 position.

The additional finding that this substance is not extractable with ether from alkalinized urine is suggestive of the presence of a carboxyl ending on the resulting chain. Whether or not this substance accounts for all or only part of the 90 per cent of administered nicotine that fails to be excreted unchanged, is as yet unknown. pages 239-240, (4666)

(4735) Finnegan, Larsen & Haag (Medical College of VA)

"Neither nicotine nor its products of combustion contribute significantly per se to the edema-producing properties of cigarette smoke, although it may definitely increase the subjective sensations of irritation." page 202, (4735)

(4736) Finnegan, Fordham, Larson & Haag (Medical College of VA)

"1. Tightness of packing of the tobacco within a cigarette can significantly alter the irritant properties of its smoke. The tighter the packing the less irritating is the smoke.

2. The irritant properties of cigarette smoke vary inversely with the moisture content of the tobacco smoked.

3. Cigarettes of the same brand may be of sufficiently uniform composition as to constituents so that no significant difference in irritant properties of their smoke can be detected.

4. The smoke from different brands of cigarettes may differ significantly in irritant properties.

5. **The hygroscopic agents, glycerine and diethylene glycol, do not per se significantly alter the irritant properties of cigarette smoke.**

6. The irritant properties of cigarette smoke directly applied are markedly greater than those of comparable cigarette smoke solutions." page 123, (4736)

(4760) Larson, Haag & Finnegan (Medical College of VA)

"1. Smoke from different types of cigarette tobaccos may differ significantly in edema-producing irritants. 2. Constituents are present in cigarette smoke, from at least certain types of tobaccos, which produce a degree of subjective irritation disproportionately greater than that which might be expected on the basis of their edema-producing properties." page 478, (4760)

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(4835) Haag, Finnegan & Larson (Medical College of VA)

"It has been shown that a significant decrease of the edema-producing irritants present in cigarette smoke can be effected by (1) limiting the number of puffs taken from a cigarette, (2) increasing the length of the cigarette and limiting the number of puffs taken, (3) attaching a filter tip of suitable design to the cigarette, provided the tobacco column of the cigarette is not correspondingly shortened, and (4) using a cigarette holder containing a changeable filter of suitable design. The practicability of applying these procedures is discussed." page 46, (4835)

Publications from New York. Most of articles were by Mulinos and his collaborators from the Department of Pharmacology, College of Physicians & Surgeons, Columbia University. Their subject was *Influence of Hygroscopic Agents and Acute Irritation by Cigarette Smoke*. Towards the end of the list below, publications from other New York clinics and laboratories are enumerated.

(3463) Mulinos & Osborne (College of Physicians & SUrgeons)

"We herewith report a successful attempt to measure objectively the irritant properties of cigarette smoke. We used the conjunctival sac of rabbits according to the technic of Hirschhorn and Mulinos. Cigarettes made with 1,3, and 5% glycerine respectively show a slight increase in irritation as the percent of glycerine increases. When di-ethylene-glycol is used, there is a slight but readable reduction in irritation as the percent increases. When the cigarette smoke is passed through mineral oil, the results are essentially the same as when water is used." pages 241, 245 (3463)

(3564) Mulinos & Osborne (College of Physicians & Surgeons)

"The irritation produced by cigarette smoke should be of great importance to the physician who has under his care the treatment of affections of the nose and throat. Offhand, it is rather difficult to place a definite value upon the importance of cigarette smoke in the production and perpetuation of these throat condi-

tions. For any one patient, however, we may assume that cigarette smoke may play some part in the pathology of the throat condition for which he has consulted his physician. The source of the tobacco, the flavoring agents, or the paper may each play its part in the qualities of the smoke. But besides these constituents of all cigarettes, there is another which has proved of interest. All cigarettes contain some agent for the maintenance of the proper moisture content of the tobacco. The present study is aimed at the two popular hygroscopic agent, glycerine and diethylene glycol, and their influence upon the irritant properties of cigarette smoke. Cigarettes identical in every other respect vary in irritating properties of their smoke, according to the type of hygroscopic agent used. Cigarettes in which glycerine is used are more irritating than when no hygroscopic agent is employed, while those made with diethylene glycol are definitely less irritating. Our results now show that, regardless of the blend of tobacco, flavoring materials, or method of manufacture, **the irritation produced when glycerine is used as the agent is substantially the same - and greater than that caused by diethylene glycol.**

Although these results apply only to our method of smoking the cigarettes, and to aqueous or oily solutions of the smoke, and although the irritation is measured upon the conjunctival mucous membrane of rabbits, the investigations of Flinn in 1935 indicate that the same relative irritation produced by these two hygroscopic agents holds also for the human cigarette smoker." pages 590-592, (3563)

(3664) Lieb, Mulinos & Taylor (College of Physicians & Surgeons)

"These experiments suggest that the vaso-constriction from a deep breath occurs on the arterial side of the capillary tuft, a fact borne out also by the marked changes in temperature of the skin. They suggest also that the phenomenon is of neural or reflex origin, and is not due to mechanical shifts of blood into the pulmonary circulation, for such shifts are prevented by the circulatory occlusion induced. Skin temperatures taken during a deep breath show a drop of from 1°C. to 3°C. Several deep breaths taken at one-minute intervals show a summation of effect, and a drop in from 1°C. to 6°C. That this can occur is denied specifically by Wright and Moffat, and implied by Maddock and Coller. The reflex mechanism has not yet been analyzed further, but may be due to one or more of such factors as alveolar stretching; to vascular reflex from pulmonary

blood pressure changes; or to the cooling effect of the inspired air." page 90, (3664)

(3785) Kesten, Mulinos & Pomerantz (Coll. Physicians & Surgeons)

"A report of several fatalities following the use of an 'elixir' of sulfanilamide made with diethylene glycol prompts this preliminary abstract of a portion of the work in progress on the pharmacology and pathology of the glycols and related chemicals. Only two studies of the toxicity of diethylene glycol appear in the literature. Von Oettingen and Jirouch found, using four mice, that minimum lethal dose was approximately 5 cc. per kilogram of body weight when given subcutaneously. Haag and Ambrose reported that the ingestion of the glycol in concentrations of 3 per cent and 10 per cent in drinking water was rapidly fatal to rats and that the minimum fatal dose for rabbits is 2 cc. intravenously. The vital organs of these animals were found to be essentially normal.

Diethylene glycol, administered to rats by mouth and to rabbits intravenously, caused extensive injury to the epithelium of the renal convoluted tubules, leading to urinary obstruction and uremia. The liver and adrenal were less regularly involved. A dose of from 1 to 2 cc. per kilogram of body weight intravenously to rabbits was required. The ingestion by rats of 0.5 and 1 per cent solutions in their drinking water in quantities of approximately 30 cc. daily per rat for from one to four or five months caused no renal or other symptoms. Three per cent (0.9 cc. per rat daily) in drinking water killed about 50 per cent of the rats within two months. Five per cent diethylene glycol (1.5 cc. per rat daily) killed 25 per cent within a week." pages 150-151, (3785)

(3875) Mulinos & Cockrill (Coll. Physcians & Surgeons)

"Studies were made on the smoking of cigarettes by means of a mechanical puffer under standardized conditions. It has been shown that cigarette tobacco acts as an efficient filter in respect to total volatile substances; solids; reducing substances to iodine solution; nicotine; acidity, (hydrogen ion concentration); and the color and clarity of the smoke solution. If the cigarette smoker does not smoke more than 2 thirds (5 cm.) of the cigarette, he avoids all changes in temperature of the smoke, and 60 to 70 per cent of the nicotine, tarry substances, acids, and volatile substances which reduce iodine." page 206, (3875)

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(3879) Shulman, Mulinos & Lieb (Coll. Physicians & Surgeons)

"These results show that a deep breath of air caused a constriction of the arterioles of the forearm; and that there is a greater and more lasting effect upon the vessels of the skin than upon those of the deeper structures." page 186, (3870)

(3975) Kesten, Mulinos & Pomerantz (Coll. Physicians & Surgeons)

"Dipropylene glycol, diethylene glycol, dioxane, carbinol, methyl carbinol and butyl carbinol when administered in adequate dosage orally or intravenously to animals cause extensive hydropic degeneration of the renal convoluted tubules, leading to uremia; less regularly, there is hydropic degeneration of the liver parenchyma. These compounds resemble each other in containing an ether linkage between glycol molecules. Ethylene glycol, ethylene glycol diacetate, and propylene glycol do not have such a structure, nor do they cause similar lesions in animals." page 465, (3975)

(3977) Mulinos & Shulman (Coll. Physicians & Surgeons)

"By means of 5 methods the vasomotor status of the hand has been studied in normal human subjects. These methods are described in detail. A deep inspiration causes marked vasoconstriction of the arterioles of the forearm and hand, but is especially marked in the skin of the fingers. The vasoconstriction from a deep breath is due to a reflex and is independent of the blood flow and blood pressure in the hand and of the temperature and moisture content of the inspired air. The constriction is exaggerated by any irritant or painful stimulus (pinch of skin, inhalation of smelling salts, tobacco smoke) which may accompany or shortly follow the deep breath." page 321, (3977)

(3983) Shulman & Mulinos (Coll. Physicians & Surgeons)

"The vasoconstriction from smoking may be due to a, irritation of the smoke; b, its nicotine content; c, mere inhalation. That nicotine is a minor factor is shown by the above experiments, and by observations of three smokers who smoked furiously and who showed nausea and vomiting but no vasoconstriction. It is concluded that the irritation and especially the deep breathing are responsible for the peripheral vasoconstriction from smoking." page 630, (3983)

(4063) Mulinos & Shulman (Coll. Physicians & Surgeons)

"Using 5 different methods, an analysis of the response of the peripheral vascular system to smoking and deep breathing has led to the following conclusions: Deep breathing alone can account for the greater part of the decreased blood inflow rate, the loss of hand volume and the drop in skin temperature of the hand resulting from the inhalation of cigarette smoke. The subjects who did not inhale cigarette smoke showed a greater vascular response on the hand from 10 deep breaths than from the puffing, and a lesser response than those who inhaled the cigarette smoke. Inhaling the smoke from denicotinized cigarettes resulted in as great and occasionally greater vasoconstriction than the inhaling of the smoke from a standard brand cigarette. The degree of response of the peripheral vascular system varies markedly among individuals and in the same subject from day to day. The vasoconstriction due to smoking lasts about 15 minutes (7 to 45). These figures are at variance with the conclusion that 'If ... a patient should smoke 1 cigarette an hour he would depress his peripheral circulation during the entire day.'" page 719, (4063)

(4369) Mulinos, Pomerantz & Lojkin (Coll. Physicians & Surgeons)

Metabolism and toxicology of ethylene glycol and ethylene glycol distillate. Reprint not available.

(3467) Wright & Moffet (NY Postgraduate Med Sch & Hosp)

"Nicotine has long been considered the most important factor in the causation of effects from cigarets. The vital consideration is not how much of this poison is in the tobacco but how much is actually absorbed through the mucous membranes and alveolar walls into the blood stream. The tobacco itself varies widely in nicotine content. For example, the average nicotine content of various tobacco is as follows: Havana tobacco, 1.5 per cent; Maryland tobacco, 2 per cent; Virginia tobacco, 6 per cent; Kentucky tobacco, 8 per cent. The amount of nicotine and other products in the inhaled smoke is influenced greatly by, first and most important, the amount of moisture present, and also the tightness of packing, the length of the cigarette and the rate of smoking. The drier the tobacco, the greater the destruction of nicotine. Dixon states that the water content of the tobacco is more harmful to the smoker than the original nicotine content. ... The

smoking of tobacco in the form of 'standard' cigarets produces in the great majority of normal individuals certain definite pharmacologic effects. ... Although not definitely proved, the evidence seems to indicate that nicotine is at least one of the toxic factors and that carbon monoxide and the products of the cigarette papers may be eliminated as offending mediums." pages 322-323, (3467)

(3558) Flinn (Dept. Physiology, Columbia University)

"An interesting case was reported by one of the doctors of a man who had gotten a 'piece of shrapnel in the lung during the war and found that he could not smoke more than 10 cigarettes of the regular brand a day. If he smoked more than this number he had a congestion of the lungs as if he had a severe cold, irritation of the respiratory tract which would require two months to clear up. When he was put on the diethylene cigarettes he increased the number smoked to 20 and 30 per day without noticing any effect on the lung tissue. An examination did not show any harsh breath sounds or any physical signs indicating an irritation or congestion in spite of the increased number he was smoking. He was changed to the glycerine cigarette without his knowing it and in a few days he had to cut down on the number he was smoking and complained of his lungs. On being put back on the diethylene cigarette the symptoms disappeared again.' We regret that the observations made by the group of 10 doctors were not in a shape to permit our tabulating them in a more scientific manner but the results remain the same. We have simply taken the clinical findings of the 10 men and analyzed them.

Summary: The combustion products of glycerine when it is used as a hygroscopic agent in cigarettes will under certain conditions cause an irritation of the throat. The combustion products of diethylene glycol cause only a slight irritation, if any, of the throat. There is some evidence that they may be beneficial where irritation is present." page 153-154, (3558)

(3775) Flinn (Dept. Physiology, Columbia University)

"The new studies reported to me by these doctors confirm my previous report. I have received similar reports from other doctors with a smaller number of observations; one of them said: 'This study of glycerine treated cigarettes shows that they produce considerable irritation to the throat and in many cases

are responsible for the paroxysms of coughing that many cigarette smokers complain of. After putting them on diethylene glycol treated cigarettes they had less throat irritation and the paroxysms of coughing promptly disappeared. In practically every case, except in those cases where there was definite pathology, my patients were markedly improved.' Laboratory and clinical studies are in agreement that cigarettes containing diethylene glycol are less irritating than those containing glycerine." page 60, (3775)

(3669) Wallace, Reinhard & Osborne (NYU College of Medicine)

"The results of the work are shown in the accompanying table and charts. From these it is seen that the agreement with those of Mulinos and Osborne is remarkably close. The correctness of their statement that the smoke from cigarets which have been made with di-ethylene glycol as the hygroscopic agent is less irritating than those with no hygroscopic agent and much less irritating than those made with glycerin is thus confirmed. Further, it may be stated that the duration of irritant effects from the cigarets treated with glycerin is much longer than that from those treated with the di-ethylene glycol. With the experimental basis thus established, the clinical results obtained by Flinn are what would be anticipated and can be accepted as correct." page 309, (3669)

(3782) Lesser; Brooklyn, NY

"Sir: Your issue of March, 1936 carried an article by three members of Philip Morris & Co. entitled "Cigarette Industry Rules out Rule-of-Thumb." In the course of it the claim was made that 'use of diethylene glycol in place of glycerine constitutes one of the major advances in recent years in the manufacture of cigarettes.' The claim rested on two sets of tests, one made in the laboratory by Mulinos and Osborne, the other clinically by Frederick B. Flinn.

In justice to your readers, they should be informed that those tests have since been duplicated by other investigators who have published their reports, and that supplementary experiments have been made. These later findings throw serious doubts - to put it mildly - upon the validity of the 'major advance' claimed by the Philip Morris representatives.

The refutation of the claims for diethylene glycol as against glycerine as the hygroscopic agent in cigarettes has been published in the following reports:

... Space in a letter does not allow a discussion of the conclusions reached by Haag, Ballenger, Johnson, Holck and Carlson, all authorities in their fields. Suffice it to say that they refute, specifically and in detail, the statements on the subject made in the article in your columns under the signatures of the tobacco company's employees. The Haag article meets the Mulinos-Osborne assertions; the others sharply contradict Flinn.

The company, for obvious commercial reasons, has continued its claim in a high-powered advertising campaign to the medical profession and the public, completely ignoring the published refutation of its contentions. Curiously enough, certain medical journals continue to publish full-page Philip Morris advertisements that make these same claims, despite the fact that the refutation is on records in the medical press itself.

But chemical engineers ought to know the facts behind the advertising. Those who read and may have accepted the Philip Morris contentions in your March, 1936 issue should, in the interest of professional objectivity, read the later developments as detailed in the reports I have listed." Letter to the Editor, Chemical & Metallurgical Engineering, page 443, (3782)

(3774) Fishbein (Editor, JAMA)

"Sir: In your August, 1937 issue, page 443, appears a letter signed by Milton A. Lesser, calling attention to some writings on the subject of cigarette smoke and its effects on the throat, which, it is claimed refute much that has previously been published concerning cigarettes made with diethylene glycol. The author of the letter sent to you is a chemist whose qualifications for judging clinical evidence are not apparent. The bibliography of Mr. Lesser, so far as it concerns glycerine, indicates that he has devoted himself largely to encouraging the use of that substance not only in cigarettes but in practically every other phase of human life. Certainly one would not be inclined to accept him as an unbiased critic in this field. Inasmuch as he has cited in his article the exceedingly brief bibliography which favors the use of glycerine glycol, it would have been much more fair to cite at the same time the bibliography of the articles prepared from a different point of view and based on far more extensive clinical evidence than is cited in Mr. Lesser's letter. The concluding paragraphs of his letter contain

an insinuation which cannot be supported by any evidence." page 501, (3774)

The four articles cited by Lesser were later acknowledged by the tobacco company. Haag's research support from the tobacco company was not cancelled because of scientific disagreement with Mulinos, Osborne & Flinn.

Publications from Illinois. The poisoning episode with sulfanilamide suspended in diethylene glycol coincidentally occurred while the glycol was being introduced as a hygroscopic agent for tobacco. In spite of animal studies denying that inhalation of diethylene glycol was unlikely to cause toxicity, the further use of the hygroscopic agent was stopped. I do not have any publication on the year it occurred. Most writers who were critical of any form of human use of diethylene glycol were from Illinois. McNally , from Rush Medical School, published the suspected effects of cigarette smoke tar in the 1930's and then joined the anti-diethylene group marked by another article in the 1940's (see also Chapter III, page 214).

(3224) McNally (Rush Medical College):

"The tar of cigarette smoke contains nicotine, phenolic bodies, pyridine bases, and ammonia, irritants which could account for 'cigarette cough,' the chronic bronchitis of the cigarette smokers, the leukoplakia in heavy smokers, and the recorded increase of cancer of the lung. The temperature is not an important factor unless the cigarette is burned down to the last centimeter, when the hot smoke becomes more irritating. With a tarry residue of 4.84 to 15.29 per cent, a definite risk attaches to the smoking of a cigarette, especially since 6.56 to 11.58 per cent may be absorbed or retained in the body. Cigarettes should not be smoked too short, as the last two centimeters retain

most of the tar and other products of incomplete combustion." page 1513, (3224)

(3773) Editorial (JAMA)

"Nine out of ten patients who had been given a proprietary elixir of sulfanilamide died recently in Tulsa.., Okla., from anuria which apparently resulted directly from poisoning by this elixir. As we go to press, the record is swelled by the report of four additional deaths with another likely fatality in East St Louis. The product was prepared and sold by the S.E. Massengill Company of Bristol, Tenn. From tests by the chemical laboratory of the American Medical Association, this elixir appears to be a solution of approximately 40 grains of sulfanilamide to a fluidounce of a menstruum containing about 72 per cent of diethylene glycol (by volume) with flavoring. Apparently it is not known whether the toxicity of sulfanilamide is enhanced by the presence of diethylene glycol - or vice versa. The solvent, diethylene glycol, is itself not an indifferent substance. While its use is not permitted in food products because of the absence of any scientific evidence establishing beyond doubt its harmlessness when taken internally, it has long been utilized as a solvent in various industrial processes. The dosage of the elixir administered unquestionably contained a large amount of this substance. It would appear to be clear that the diethylene glycol or the diethylene glycol-sulfanilamide combination rather than the sulfanilamide was responsible; one of the patients had received tablets over a period of two weeks without any bad effects and then showed the typical train of symptoms after taking the elixir. From twenty-four to forty-eight hours after administration of the substance, nausea, vomiting, malaise and sometimes diarrhea developed; then complete anuria appeared within two to five days. The nonprotein nitrogen, urea nitrogen and creatinine rose rapidly. In the postmortem examination there was usually an accumulation of fluid in the serous cavities, with degeneration of the tubules of the kidney and a peripheral necrosis of the liver." page 1367, (3773)

(3778) Holck (University of Chicago)

"The results of these experiments place diethylene glycol between ethylene glycol and propylene glycol in toxicity. A high concentration of glycerin in the solid food (20 per cent) seemed harmless. Diethylene glycol in one fourth of this concentration in the fox-chow and in

much smaller concentrations in the drinking water was distinctly harmful as judged by cases of mortality, stunted growth in the young, and impaired reproductive capacity. ... In an eleven weeks experiment, younger adult female rats gained about he same in body weight as control animals when a high concentration of glycerin (20 per cent) was mixed with their solid food. Similar concentrations of commercial diethylene glycol killed all rats within about two weeks, and even 10 and 5 per cent proved fatal to some of the rats. Diethylene glycol is even more toxic when added to the drinking water. When the rats drank from a 5 per cent solution, the average duration of life was only eight days." page 1519, (3778)

(3779) Holck & Carlson (University of Chicago)

"Our data give no indication that cigarettes can be classified consistently as to the irritating quality of the smoke by supposedly normal humans, although Flinn's report suggests patients with various affliction due to smoking are able to judge differences in cigarettes similar in nature to ours. In many cases the same kind of cigarette was at one time called mild and at a subsequent period pronounced irritating by the same person. We believe, therefore, that a method for determining the irritating properties of cigarettes which relies solely upon the opinions of ordinary smokers cannot be considered reliable. The smoke of these 3 types of cigarettes increases the acidity of water to an equal extent, as determined by exact pH tests." page 307, (3779)

(3792) Schoeffel et al (AMA Chemical Laboratory)

"Elixir of Sulfanilamide-Massengill in the specimens examined was found to consist essentially of sulfanilamide 10 Gm. in 100 cc. of a solution of approximately 72 per cent diethylene glycol and water 25 per cent by volume, to which had been added flavoring and coloring material. Diethylene glycol in the doses given was the causative agent in deaths. Pathologic results reported herewith both on animal and on man, as well as many reports received by telephone and telegram, indicate that, in cases of death following the administration of Elixir of Sulfanilamide-Massengill, anuria was present." page 1539, (3792)

(3795) Ballenger & Johnson (Northwestern Univ. Med. Sch.)

"From a clinical study of the personnel forming the basis of this investigation, it is concluded that the hygroscopic agent used in cigarets is not a factor of importance in producing symptoms or in producing objective evidence of irritation of the nasal or throat mucosa or of the conjunctival sac. In fact, the control cigarets, in which no hygroscopic agent was used, seemed to produce somewhat more irritation both objectively and subjectively than those to which glycerin or diethylene glycol was added." page 80, (3795) Authors acknowledged grant from Glycerine and Soap Manufacturers Association

(3873) Geiling & Cannon (University of Chicago)

"The intelligent, energetic and cooperative manner in which the representatives of the American Medical Association, of the Food and Drug Administration, of the U.S. Department of Agriculture and of cooperating educational institutions worked brought this episode to a speedy solution. Had it not been for their splendid service the toll of human life would probably have amounted to several hundreds." page 926, (3873)

(3967) Ballenger (Northwestern University Medical School)

"Careful objective examination failed to show any significant difference in irritation of the mucosa of the nose or throat by cigarets moistened with glycerin, those moistened with diethylene glycol or those with no hygroscopic agent. The subjective symptoms or sensations of irritation, when present, were not marked enough in respect to distribution, character or degree to justify definite conclusions. Lymphoid hyperplasia of the pharynx does not appear to have any relation to the number of cigarets smoked." page 123, (3967)

(4332) Fabricant (Univ. Illinois College of Medicine)

"A method is described involving minute to minute readings of the pH values of the mucous membranes of the human throat for studying the irritating effects of cigarette smoke. The pH range of the clinically normal throat was found to vary from 4.9 to 8.0, the reaction in the majority of cases falling within the acid range. While the values varied with different persons, for the same subject the range was small and fairly constant. Cigarette smoke, regardless of the kind of cigarette, in

openly asserts that there are no differences in the irritating properties of the various types of cigarettes now available to the American smoker. Further, there is no indication that cigarettes can be classified consistently as to the irritating quality of the smoke by supposedly normal human beings. In many instances, it has been demonstrated that the same kind of cigarette has at one time been called mild and at a subsequent period been pronounced irritating b the same person. In fact, a method for determining the irritating properties of cigarettes which relies solely upon the opinions of ordinary smokers cannot be called reliable. Patients, including physicians, will continue to smoke because they gain some pleasure from the habit, actual or imaginary. The only advise one can give conscientiously of that of moderation. There is no scientifically valid 'health' story when it comes to the subject of irritation." pages 312-313, (4622)

(4634) Holinger et al (Chicago)

"As a result of the measurements of blood vessels on 544 photographs of the uvula and soft palate of 136 subjects, the following observations were made: In a series of photographs of 12 subjects the measurement of the 105 measurable blood vessels showed that diethylene glycol treated cigarettes had a greater dilating effect on the blood vessels of the uvula and soft palate than either glycerine treated cigarettes or cigarettes containing no hygroscopic agent; however, the differences were so small that they were not statistically significant. ... The possible correlation between the effects of smoking on blood vessel diameter and the irritating properties of the smoke is discussed and it is concluded that the conflicting effects of some of the smoke constituents invalidate methods for evaluating smoke irritation which depend on measurement of blood vessel diameter or the attendant gross color changes." pages 778-779, (4634) Grant from Association of American Soap and Glycerine Producers, Inc.; also used in FTC Hearings, Docket No. 4794.

(4712) Andrews, Lenth, Staunton & Holinger; Chicago, IL

"The correlation between the reflectance readings and changes of color of the pharynx is discussed and it is concluded that the changes in reflectance probably are the result of changes in color, but that the evidence is insufficient to justify a more positive statement due to the possible complications introduced

by unknown changes in the film of mucus on the pharynx; however, if the measurements represent color, the average effect observed was that of blanching rather than reddening." page 225, (4712) Grant from Association of American Soap and Glycerine Producers, Inc.; also used in FTC Hearings, Docket No. 4794, its purpose unclear.

(4549) McNally, Bergman & Foster; Chicago, IL

"Experiments were performed on the irritating properties of smoke from tobacco treated with glycerine and diethylene glycol using the technique of Mulinos and Osborne. We could find no significant difference between the smokes from these two types of tobacco or between either of these and the smoke from plain tobacco." pages 251-252, (4549) Data have been used in court testimony, its purpose unclear.

Publications from District of Columbia, Missouri and Delaware. The diethylene glycol poisoning episodes led to articles written by personnel of the Food and Drug Administration. Laryngologists from Missouri contributed to the growing literature on irritant action of cigarette smoke:

(3976) Laug, Calvery, Morris & Woodward (FDA)

"The relative acute toxicities of some glycols and derivatives have been determined and the order of increasing toxicities is as follows: propylene glycol, diethylene glycol, ethylene glycol, diethylene glycol mono-ethyl-ether dioxin, and ethylene glycol mono-ethyl-ether. Three species were used: rats, mice and guinea pigs. A limited number of rabbits were used on diethylene glycol. The total number of animals used was over 2600. The rabbits, in comparison with other species, were found to have the lowest LD 50 for diethylene glycol. In fact, the lowest dose that killed some rabbits was the same as the estimated average dose that killed 105 persons." page 197, (3976)

(3986) Calvery & Klumpp (FDA)

"In September and October, 1937, approximately 203 gallons, of a total production of 240 gallons, or a proprietary remedy, 'elixir sulfanilamide,' was distributed. It was composed of 72 per cent diethylene

glycol, 8 per cent sulfanilamide, and 20 per cent of essentially flavors, saccharin, caramel and water. Each fluid ounce contained, therefore, approximately 21.5 cc. of diethylene glycol and 2.7 grams of sulfanilamide. The data on 105 deaths associated with the consumption of this drug are available for toxicologic study. In addition, reports concerning 248 individuals who consumed varying known amounts of the drug but survived are also available for study. The information which serves as the basis for this report was obtained principally from physicians, patients and relatives, and by the inspectors and scientific personnel of the Federal Food and Drug Administration. In addition, collateral and supportive data were obtained through the generous cooperation of pathologists, pharmacologists, and the American Medical Association, by whom various aspects of the mass poisoning were likewise studied. A number of reports relating to the tragedy have already been published. A study of the literature on human toxicology reveals few reports of mass poisoning of similar magnitude.

Consideration of clinical experience with sulfanilamide, pharmacologic and toxicologic studies of both diethylene glycol and sulfanilamide, and study of the pathology of fatal cases of 'elixir sulfanilamide' poisoning leads to the inescapable conclusion that the poisonous ingredient in the 'elixir sulfanilamide' was diethylene glycol. It is unlikely that the sulfanilamide contained in the preparation had a determinative deleterious effect in the majority of the cases. On the other hand, it is not unreasonable to suppose that the presence of sulfanilamide placed an added burden upon organs already damaged by the diethylene glycol." page 1105-1106, 1008, (3986)

(4247) Morris, Nelson & Calvery (FDA)

"The results of this investigation illustrate clearly the advantage of the long-time chronic toxicity study. The results obtained by continuing the experiment for two years that would not have been noted if it had been discontinued at the end of one year were the occurrence of urinary calculi in each of the series of the animals receiving ethylene glycol and diethylene glycol. It is possible also that the microscopic lesions and testicular enlargement observed would not have been as distinctly different between the experimental and control animals if the experiment had been continued for only one year. As we have emphasized elsewhere chronic toxicity studies should be continued

over long periods of time especially in the case of those substances that are to be included in the diet of man or are to be administered as therapeutic agents or applied as cosmetics repeatedly over long periods of time." pages 271-272, (4247)

(4624) Fitzhugh & Nelson (FDA)

"Bladder tumors occurred in about half of the rats on the 4 per cent and 2 per cent concentrations, and in none of those on the 1 per cent concentration of diethylene glycol. The tumors of the bladder were both papillary and intramural. The former were generally benign, while some of the intramurally located tumors showed varying degrees of malignancy. On the 4 per cent level of diethylene glycol in the diet, lesions in the kidneys of rats were moderate to marked in degree, on 2 per cent they were slight or absent. Eight of the 12 rats had kidneys which were hydronephrotic, enlarged, fibrous, granular or combinations of these. Microscopically, the chief lesions were varying degrees of focal tubular atrophy and hyaline case formations." page 43, (4624)

(3978) Proetz; Washington Univ. Sch. Med., St. Louis, MO

"Regarding the reliability of simple clinical observation as a basis for statistical studies of the pharynx, even under the best conditions and with the problem clearly defined in the mind of the examiner, we find a diversity of opinion reaching 70 per cent. Regarding the comparison of subjective irritation with objective changes, as seen in the clinic, we find a discrepancy in 54 per cent of the cases, when these are divided into four broad categories. Even when they are divided into two classes, 'obviously inflamed' and 'obviously not inflamed,' the discrepancy still reaches approximately 7 per cent. Just what are the objective changes produced in the mucosa by the protracted action of cigarette smoke has not been determined. It is not at all certain that they may be classified in terms of color, or even that progressive irritation results in progressively heightened color. It would of course be desirable, in the light of the minute changes which are likely to occur, to eliminate the human element as much as possible in recording them. Whether a colorimeter can be devised which will provide a graphic record of small, variously colored areas of the mucosa and whether after that, one can learn to interpret such a record in

terms of cigarette-smoke-effect remains to be seen." page 194, (3978)

(3979) Proetz; Washington Univ. Sch. Med., St. Louis, MO

"We had to devise some means also for getting hold of the tar so that we could apply it in some sort of standard way to a human throat. It is going to have to be done in a large series of cases. **We have already made something short of 1,300 observations only to conclude that routine human observation of the throat is not very reliable.** We have devised a colorimeter which will measure accurately the color changes in the throat because we do not know for what we are looking. We do not know that the initial change may not be a paling instead of a reddening. There may be an astringent effect first or last. At any rate there are certain effects that we have noted that we can put to use. For instance, we will make use of what is known as the impingement effect to collect the tar from the cigarette. I will show you how it works. If we blow the smoke from a cigarette through a glass tube, against a sheet of paper, practically none of it sticks, as I told you before in regard to the little white paper box. However, if we blow it with some force through a capillary tip, so that eddies are formed, the tar is forced against the paper more or less forcibly and sticks there and can be gathered. That is the principle, of course, utilized in the cigarette holders employing a cigarette as a filter. It is simply a series of capillary tubes. However, we have rigged up a contraption of glass tubes, so that the smoke which we are studying can be deposited right on the tip of a glass rod. We can pile up the tar and gather the fumes in balloons and apply them to the throats of human subjects. As I said before, there are many variable factors that control the color changes in the throat, the temperature of the room, the condition of the climate, the patient's condition of health, the patient's recent eating of a meal, the patient's having a cold, and what not, so that literally thousands of these tests will have to be made before we can arrive at anything of scientific value. If these very few short descriptions of a laborious job are of any value at all, it is probably to point out that the problem is an involved one and that one must investigate the source of any statements made about tobacco smoking before giving them any credence." pages 245-246, (3979)

The last pertinent article on ethylene glycol was by Wiley, Hueper, Bergen & Blood from the Haskell Laboratory of Industrial Toxicology, DuPont, Delaware. They reported the formation of oxalic acid following oral administration in dogs (3853). Hueper continued his interest in toxicity of urinary system by describing chronic bacterial cystitis in the dog (4147) and pursuing further mechanism of urinary bladder carcinogenesis (see above, page 423).

Constituents of Tobacco Smoke

Prior to the 1940's, the most comprehensive review on the biochemistry of tobacco was by H. Bruckner, from Berlin (3657). This article, as well as 3 other German articles on nicotine (3565) (4346) (4464) need English translation because it would be important to evaluate the opinion of Bruckner and other German chemists on suspected carcinogenic action of tobacco smoke. There were publications on constituents of cigarette smoke such as acid bases, ammonia oxides and alkaloids (3569) (3655) (3768) (3769) (3971) (4894) (4932). A comprehensive review on constituents of cigarette smoke was not available in English during the 1940's.

Nicotine content. Jensen and Haley, from the Pennsylvania Agricultural Experiment Station, was one of the early American tobacco chemists who measured the nicotine content of cigarette smoke generated by a machine (3561). They concluded that

nicotine content varied inversely as the moisture content of cigarettes. They also reported that nicotine content in side stream smoke varied with moisture content. The nicotine content was also influenced by portion of tobacco used for manufacture of cigarette (3560), and manner of curing tobacco leaf (3659) (3660) (3794).

Health effects of nicotine. From the time leaf tobacco was sold on the auction floor until it was finally made into a cigarette, a number of manufacturing operations occurred, including steaming and redrying of the leaf (4896). McCormick, Smith and Marsch from North Carolina State Board of Health studied the health hazards in tobacco industry:

> "The results of the study indicate that certain health hazards may exist in industrial establishments engaged in processing leaf tobacco. Of these, those due to the inhalation of free silica and insecticide dust are probably of most importance. This statement is made with the realization that at the present time insufficient evidence exists relative to the hazard associated with the inhalation of nicotine. Only the nudging-blending, stemming, and cleaning operations were found to present health hazards. A tentative maximum allowable concentration of total dust of 10 MPPCF is suggested. The maintenance of atmospheric dustiness below this value should control satisfactorily all of the other associated health hazards. The free silica content of dusts found in these processing plants ranged from approximately 22 per cent to 58 per cent by weight, with no significant difference between the various operations studied. A significantly lower free silica content of atmospheric dust than settled dust was observed. The Goldman modification of the hydrofluosilicic acid method of free silica analysis compared favorably in accuracy with the X-ray diffraction method. The geometric mean particle sizes of the atmospheric dust showed average values of 0.90, 0.79, and 0.85 microns respectively for the hanging-blending, stemming, and cleaning operations. Respective standard deviations

of 2.86, 3.18, and 2.68 for these same operations were found. These results indicate that the atmospheric dust is hygienically significant and within the size range of industrial dusts." page 51, (4896)

Harris enumerated in his SOA report the following health effects of nicotine unrelated to suspected carcinogenic action: coronary heart disease (3459) (4035) (4122) (4652); peripheral vascular disease (3470) (3654) (3880); disturbances in reproduction (4357), pregnancy (2960) (3567) (4033) (4165), breast feeding (4252); and difficulty in stopping cigarette habit (3661) (4150). These articles are recalled here to emphasize that prior to 1950, there was no published suspicion that nicotine caused cancer.

Physicians Against Cigarette Smoking

There were three lay publications that discussed the background of physicians and scientists who joined the anti-smoking movement: Kenyon, from Axton-Fisher Tobacco Company, Louisville KY (3405); Porter, from a Southwestern College of Mines and Metallurgy (4755); and Gottsegen, an economist from Columbia University (4004). The latter author discussed in *Tobacco*, not only its consumption in the United States, but alleged health effects of tobacco, including cancer of lips, tongue, mouth, throat, lungs and esophagus. The title of the book probably misled Larsen, Haag & Silvette and was omitted in their *Tobacco Monograph* (6101). The pertinent quotations from Gottsegen is included in the list below as examples of prevalent

opinion prior to 1950. Physicians who were discouraging tobacco smoking for medical reasons based their opinion on reportedly high incidence of coronary heart disease among cigarette smokers. Cancer was rarely mentioned other than that tobacco smoke was one of several "irritants" suspected of causing cancer.

(2301) Kellogg; Superintendent, Battle Creek Sanitorium and Editor of Good Health:

> "Besides the nicotine there are all the other poisonous products which are always present in smoke, creosote, pyridine, prussic acid, furfural. The complacency with which smokers and sometimes non-smokers, ladies, perhaps, often sit for hours in a room the air of which is blue with tobacco smoke, is an evidence of the blunting effect of nicotine upon the normal sensibilities. Smoke from any other source would not be tolerated. Yet smoke is smoke, and tobacco smoke does not differ essentially from other smoke except by the addition of nicotine, and other poisons much worse than those of ordinary smoke. The well-known irritating effects of smoke upon the respiratory membranes easily explain the injurious effects from tobacco smoke observed in the throats of smokers. Smoker's sore throat is a condition very familiar to throat specialists. The highly irritating and injurious effects of tobacco smoke in cases of chronic disease of the throat and lungs from other causes is also well known. So long as the patient continues to smoke his throat maladies are incurable; but from the moment he lays aside his pipe or cigar, recovery begins." pages 49-50, (2301)

(2632) Rolleston; University of Cambridge

> "The medical aspects of tobacco interest us all in our capacity as medical advisers of others, and, in addition, probably a certain proportion from a personal point of view. As in the case of alcohol, our opinions are inevitably colored by our own tastes, for the teachings of the laboratory cannot always be rigidly applied to human practice or correspond with the empirical lessons of a lifetime. Animal experiments cannot well take into account idiosyncrasies, and with regard to alcohol and tobacco personal peculiarities are so important that they must often over-rule any hard-and-

fast laws. ... On the respiratory tract, tobacco-smoking is responsible for pharyngeal catarrh which may spread to the larynx and bronchial tubes, causing cough, hoarseness, bronchial catarrh, and so emphysema of the lungs. **The irritating effect on the throat and upper air passages exerted by cigarette smoking has been ascribed to furfural, pyridine, and ammonia, and not to nicotine."** pages 961, 965, (2632)

(3047) Rolleston; University of Cambridge

"Tobacco and Public Health. While in Britain tobacco like alcohol has received rather a 'step-motherly' treatment in most text books on public health, more attention has been given to the subject in the United States where such well known writers as Milton J. Rosenau and Park devote considerable space to tobacco in their text books, emphasizing the fact that tobacco is in no way an aid to health. Fisk writing in Park's text book, claims that if the sedative effects of tobacco are real and dependable they should be made available in exact dosage and applied therapeutically, whereas if they are not real and dependable in a medical sense they are not real and safe as a mere drug indulgence. In view of the difficulty in determining years in advance whether an individual possesses sufficient resistance to make 'moderate' smoking comparatively harmless, Fisk recommends that the smoker should undergo a thorough physical examination periodically in order to detect any ill effects of tobacco on the circulation. Lickint has recently made enquiries of 100 men over 90: (1) whether they had ever smoked; and (2) whether they still continued the habit with the following results: - This table shows that 22 per cent. of the men over 90 had always been non-smokers, while 36 per cent. had always been smokers. Lickint's investigations during the last few years have shown that the percentage of non-smokers in the male sex has ranged from 5 to 8 per cent. The large number (64) of old men who were not smokers was due to the fact that with increase in age many lost their taste and toleration for tobacco. Most of the old smokers used pipes, a smaller number cigars and pipes and a few only cigars, but none of them smoked cigarettes, which is to be explained by the fact that on the introduction of cigarettes into Germany the men were already too old to change their habits. None of them inhaled. Lickint maintains that as inhaling is generally regarded as the most injurious form of smoking the prognosis of duration of the life of most smokers today is less favorable than before, in view of the

large proportion of cigarette smokers who practice inhaling." page 185-186, (3047)

(3569) Sharlit; New York

"The medical profession, if it is to concern itself in the matter at all, should take the following position regarding cigarettes: Tobacco smoke cannot be considered harmless. The manufacturers of tobacco products are to be encouraged in their efforts to modify the art in behalf of a more harmless smoke, but, however good the achievement, the introduction of a filtering material into the smoke stream will effect a still safer smoke. The profession should assist in the production of a consumers' psychology sympathetic to the introduction of filters into cigarettes. The physicians of the United States never have endorsed a tobacco product and probably never will, but they should be prepared to endorse and encourage the use of principles in the practice of the art where it is evident that such practices lead to the production of a less harmful smoke." page 116, (3569)

(3663) Ingalls; Associate Editor, Scientific American

"What, then, of smoking? Has science an answer to the question whether smoking is harmful? How much ought an individual to smoke?

Science need not answer these questions for they have already been answered by tests on more than 100,000,000 guinea pigs - those of us who smoke. Most smokers - probably all smokers - are doubtless harmed to some extent, usually not great, by smoking. Likewise, most or nearly all smokers derive some pleasure and satisfaction from smoking. As Professor Mendenhall says, a packet of cigarettes is a 'packet of rest,' and the same is true of cigars and the pipe. That is, tobacco is a mild sedative - it quiets our nerves. Most of us contrive, generally without thinking, to adjust the extent of our smoking in such a way as to make a net gain of smoking satisfaction over smoking harm. The few who do not, do not employ their entire intelligence or else they are too weak to do so even when they sense its need. As it probably will do little or no good to preach to this minor fraction, we pass on. The average intelligent smoker senses when he is smoking too much, because he does not feel well, and he eases off, often unconsciously. Scientific experiments, then, are interesting, and the findings derived from them provide us with something interesting to talk about with other

smokers while we smoke. But the human race has already tried out the tobacco experiment and finds perhaps something like this: smoking does not do a great deal of good but it does not do a great deal of harm. Most members of the same race, smokers included, would also agree that smokers in general would be much more widely tolerated by other members of it if they would bury their butts six feet underground." page 355, (3663)

(3789) Rolleston; London

"At the opening meeting of the session on Oct. 6th, with Dr. J. H. Pendered, the president, in the chair, a paper on the *Tobacco Problem* was read by Dr. J. D. Rolleston (London), who maintained that the subject of tobacco-smoking should be quite as much a concern of public health as the acute exanthemata, diphtheria, the continued fevers, and other forms of infectious disease - a view which appeared to be gaining ground in Germany, where many public health authorities were of opinion that the damage due to nicotine was as great as that caused by alcohol. In this country, however, the tobacco problem like that of alcohol did not seem to have received any recent recognition in public health circles. Apart from the Society for the Study of Inebriety and Drug Addiction, the subject of smoking, of which the late Prof. W. E. Dixon of Cambridge had said that the medical profession could occupy itself with none more important to the nation, like until recently any aspects of the sexual question, had been taboo in medical societies. Dr. Rolleston dealt with the incidence of smoking in different countries and religious denominations, and drew attention to the prevalence of the habit in school-children of the continent, especially in Holland and Soviet Russia. He was inclined to regard smoking as an addiction, if Dr. E. W. Adams's recent definition of addiction be accepted as 'a state of bondage to a masterful drug, manifested by craving, tolerance, intense discomfort of a specialized character on withdrawal of the drug and a tendency to relapse.'" page 908, (3789)

(3790) Rolleston; Western Hospital, London

"Kulbs attributes the recent great increase in smoking in Germany, especially of cigarettes, to the much greater devotion than in the past of the German youth to sport, which diverts them from alcohol, but attracts them to nicotine, in spite of its deleterious effect upon their athletic capacity. In an inquiry made

in the United States by Karp among twenty-four smokers as to why they smoked, thirteen replied that it was merely for the pleasure of it, six put forward its soothing and restful action, and five maintained that it promoted sociability. It is probable, indeed, that many indulge in the habit, not because it gives them any pleasure, but from a reluctance to appear conspicuous, eccentric or self-righteous by their abstinence. The influence of the massive suggestion exercised by the ubiquitous advertisements of different brands of cigarettes must also not be forgotten." page 44, (3790)

(3791) Rolleston; Western Hospital, London

"Respiratory System. - Medical opinion is divided as to the effect of the tobacco habit on the respiratory system. Lambert Lack, for instance, in 1905, and Johnson, in 1929, were inclined to the view that the evil effects of smoking on the throat has been greatly exaggerated, and maintained that the chief effect of tobacco was a local one exerted mainly on the pharynx, less frequently on the larynx, exceptionally on the trachea, and seldom, if ever, on the lungs. On the other hand, Hanau declares that nicotine has not only a superficial caustic action on the mucous membrane of the respiratory tract, but also a deeper action on the bronchial wall, vessels, nerves and smooth muscles when the smoke is inhaled. Chronic bronchitis, bronchospasm and a relaxed condition of the bronchi are also attributed to the inhalation of cigarette smoke by Hildebrandt. As the effect of smoking is irritation of the larynx and bronchi, and its antiseptic action is practically nil, Pouey maintains that the tuberculous patient should be strictly forbidden to indulge in the habit. On the other hand, Duboff found that laryngeal complications in pulmonary tuberculosis were not more frequent in smokers than in non-smokers." page 465, (3701)

(3871) Boland; Guy's Hospital, London

"You will find no difficulty in finding plenty of poems and essays singing the praises of tobacco. On the other hand, you will seek in vain for any books written in defence of it, although books written to condemn it are legion. This disparity is produced as evidence by one of the spokesmen for the anti-tobacconists. He said that this showed that there was no case to be made out for tobacco, and that this proved its badness; but the smoker is, perhaps to his detriment, a philosophical

person; he seeks no converts, and in the face of all fulminations continues to smoke his pipe in unruffled peace. You will notice, therefore, that all the books which are written about tobacco are, in fact, written against tobacco, and you will look in vain for any dispassionate study unless you can find impartiality in M. Poucel, who starts his books by saying that he will consider the question without bias and without any preconceived prejudice, and then refers to it as 'This scourge ...' on about the third page! All writers appear to be singularly unanimous not to say imitative in their charges against tobacco. I will endeavour to summarize them, as it would take much too long to recapitulate all of them. **Starting with the respiratory system first of all, they state that it produces chronic laryngitis, chronic bronchitis and all the complications that come in its train; that it aggravates the disease of the tuberculous and predisposes them to tuberculous laryngitis, and that it may be an important factor in the production of growths of the lung."** page 226, (3871)

(3973) Harris; President, Alabama Med. Assn,, Birmingham, AL

"When the effects of tobacco on the human body are considered, and also the fact that every smoker, during the twenty or thirty years while he poisons himself slowly with nicotine, contributes at least $1,000.00 to plutocratic tobacco manufacturers, it is evident that Barnum's estimate of a sucker result of the high powered advertising campaign to teach women and girls to smoke, the use of cigarettes has increased ten fold; and an estimate of 'a sucker born every second' does not over-estimate the number of gullible men, women and children who have 'swallowed the bait, hook and line' of tobacco manufacturers. Tobacco would not be used by civilized people if it were not that the manufacturers and advertisers of cigarettes and other forms of tobacco propose to make money, without regard to whether or not the product they manufacture and advertise is harmful to, and shortens the life of, those who form the nicotine habit. The young physician, before he becomes an abject slave to tobacco - and therefore incapable of forming an unbiased opinion on the physiologic and pathologic effects of nicotine - should study recent clinical investigations regarding tobacco as a cause of disease. In making his case histories he should record the number of cigarettes, or the amount of tobacco in any form which the patient uses, and then try to per-suade the victim to give up tobacco. Usually he will

see marked improvement in those who are wise enough to follow his advice; and, if he is not a tobacco addict himself, he will find what a 'strangle hold' tobacco has on the great majority of its victims, many of whom admit that they would risk being sick, or hazard life itself, rather than give up the use of tobacco. When the above facts are remembered, Professor Raymond Pearl's studies are even more convincing that the use of tobacco, even moderately, decreases longevity and that the excessive use of tobacco shortens life very materially." pages 281-281, (3973)

(3974) Head; Northwestern University Medical School

"As vices go, it is probably comparable to the common cold among illnesses. But the common cold, while not threatening life, is, because of its prevalence, a very important disease, accounting in the aggregate for a tremendous loss of working time and a still greater loss of working efficiency. Smoking similarly, while rarely causing serious consequences, certainly is a bad thing for the individual and for the race. **It is not an especially strong habit.** While it is uncommon to find anyone who inhales who stops permanently, many do stop for long periods. Those who stop permanently do so usually because they have been frightened by symptoms attributed to smoking. Deprivation causes discomfort but no serious manifestations." page 285, (3974)

(4004) Gottsegen; Columbia University, New York, NY

"However, **smokers are not more susceptible to cancer of lips, tongue, mouth, throat, lungs and esophagus. Tobacco acts only occasionally as an irritant and is not necessarily a determining factor. This conclusion is corroborated not only by clinical evidence but also by statistical data.** In those parts of the world, where women are heavy smokers, as in Brittany, Holland, Asia and Africa, cancer of the tongue is not more frequent in women than elsewhere. Moreover, despite an increase of smoking, there is no similar increase in mortality from cancer of tongue, lip, mouth and jaw. In 1934, the New York City Health Department also reported a decrease in the number of the above types of cancer for women." page 94, (4004)

(4064) Myers; Kansas City, MO

"Improved methods of diagnosing, instead of inhaling smoke, may explain the constantly increasing

number of patients found suffering from cancer of the respiratory tract. Though literature reveals that for certain individuals smoking is injurious, much more work must yet be done to prove that the abnormal actions of organs, produced by nicotine and other chemicals found in smoke, are lasting. Medical and other researchers who are seeking the truth on this subject are increasingly calling attention to the damaging effect on the human body produced by smoking, and especially by inhaling smoke. Because of the carcinogenic action of tar found in tobacco smoke there is need for the closest observation of the air passages, and most skillful diagnostic acumen when patients habitually smoking and inhaling, present themselves for medical care." page 349, (4064)

(4133) Crampton; U. S. Army, New York, NY

"The use of cigarettes has increased eleven times since the beginning of the world war. It is still increasing. Soldiers smoke more than civilians. This will probably lead to an even larger per capita consumption of cigarettes in the near future. The toxicity potential of smoking is a matter important to the physician, both military and civilian. The physician must recognize smoking as a general human phenomenon. He must be understanding and deal with the problem accordingly. The physician who expects co-operation when modifying his patients' smoking, must consider the 'pleasure factor.' It is important not to lose sight of the fact that people smoke for enjoyment. It is also evident that smokers cannot be diverted to any great extent to cigarettes which are lacking in this respect, either because of special processing, for hygienic purposes, or due to a deficiency in inherent quality. General prohibitions are not indicated. A final complete answer is yet to be formulated, and it should be reasonable, scientific, and above all, human-wise." page 11, (4133)

(4240) Johnston; Wallasey, GBR

"Nicotine was given hypodermically, in doses ranging from gr. 1/50 to gr. 1/10, to 35 volunteers, some being smokers and others non-smokers. Symptoms induced by the injections were described as 'swimminess' or 'muzziness'; large doses caused toxic symptoms in addition, including rapid and forcible cardiac action, vomiting and syncope. Smokers could tolerate considerably larger doses than non-smokers. Intravenous

(4456) Maris (affiliation unknown)

"Pictures showing wounded soldiers lying on cots or stretchers smoking cigarets dramatize the important fact that nothing is left undone to improve the morale of our fighting men. Yet these same pictures may do a disservice to Army doctors, for if the wound involves the circulation, particularly of the arms or legs - and most war wounds do - the chances are the soldier wouldn't be smoking." page 740, (4456)

(4461) Morton; Middlesex, GBR

"The incidence of bronchitis, atelectasis and broncho-pneumonia after abdominal operations and 'gas-oxygen-ether' has been studied in 1257 cases in adults. The use of omnopon-scopolamine, a mild respiratory depressant, for premedication was associated with a slight but not significant increase in pulmonary complications, as compared with the use of atropine alone, which has no depressant effect. The combined figures for all types of abdominal operations show that the morbidity-rate for smokers taking more than 10 cigarettes or 1/2 oz. tobacco a day is about 6 times that for non-smokers. Smokers are more likely to develop complications associated with serious constitutional disturbance." page 370, (4461)

(4827) Editorial; JAMA, Chicago, IL

"For some years *The Journal of the American Medical Association*, the state medical journals and most other medical publications have carried the advertisements of the various companies that manufacture cigarettes. Actual surveys indicate that the majority of physicians themselves smoke cigarettes. Extensive scientific studies have proved that smoking in moderation by those for whom tobacco is not specifically contraindicated does not appreciably shorten life. Postmortem examinations do not reveal lesions in any number of cases that could be definitely traced to the smoking of cigarettes. From a psychologic point of view, in all probability more can be said in behalf of smoking as a form of escape from tension than against it. Several scientific works have been published that have assembled the evidence for and against smoking, and there does not seem to be any preponderance of evidence that would indicate the abolition of the use of tobacco as a substance contrary to the public health. Physicians are no doubt familiar with the articles that have been

> published on the effects of tobacco on the circulation, the blood, the gastric acidity and other physiologic mechanisms within the human body. This editorial will not attempt to summarize the evidence or to derive any positive conclusions from it. It is concerned, rather, with the manner in which leading manufacturers have begun to lean so heavily on reference to the medical profession in promoting their products.
>
> The advertising accepted by *The Journal of the American Medical Association* has always been screened through various committees, and the evidence in behalf of the statements made has seemed to be sufficient to warrant the statements that appear in the advertisements. Gradually, however, claims point more and more toward the single factor of the extent to which certain cigarettes irritate the throat. One product is said to be less irritating than others, and the suggestion is made that persons who suffer irritation from other cigarettes try the one that is said to be less irritating. Another is said to be always milder; a third is said to be absolutely free from throat irritation as based on tests conducted under the supervision of physicians." page 652, (4827)

Most of the above are derived from Harris' selected references. However, I have selected sentences that do not necessarily support Harris' summary statements. Instead, the quotations imply that tobacco smoke is a general "irritant" which was the subject of research projects supported by tobacco companies. Since "irritants' are suspected to be a cause of lung cancer prior to 1950, the tobacco companies cannot be criticized for misdirected research funds.

D. OCCUPATIONAL/ENVIRONMENTAL FACTORS

Prior to 1950, there was considerable literature supporting the causative role of occupational exposure and environmental factors in lung cancer patients. During the 1940's, there were more medical researchers who studied non-smoking causes of lung cancer, than those who published articles blaming cigarette smoking as the cause. The situation can be summarized as follows: First, the appearance of monographs, review articles and original studies on occupational and environmental carcinogens far exceeded those suggesting cigarette smoking or other personal habits as cause of cancer; Second, majority of clinical articles on lung cancer that mentioned cigarette smoke as an associated factor also discussed the coincidental association with occupational and environmental factors; Third, some constituents of coal tar that were chemically isolated, synthesized and tested for animal skin carcinogenicity, were also detected in cigarette smoke leading to a conflicting interpretation of relevance of animal skin painting to human lung cancer; Fourth, some industrial chemicals that were suspected human carcinogens were also detected in cigarette smoke and this contributed to further suspicion that cigarette smoking caused lung cancer without considerations of relative concentrations between work environment and cigarette smoke; and Fifth, the animal and human observations incriminating fossil fuel products and vehicular combustion emission as pulmonary

carcinogens were already known prior to 1950 and were reinforced by additional studies from 1950 to 1966. The acceptance of cigarette smoking as a cause of lung cancer in a particular patient continued to be challenged by coincidental exposure of the patient to occupational/environmental factors.

Monographs on Occupational Cancer

In the *History of Cancer Control in the United States, 1946-1971*, Agran reviewed the history of cancer in workers starting with the 1775 discovery of Percival Pott of scrotal cancer among chimney sweeps (7701). Pott's findings coincided with the onset of the industrial revolution and was followed by discoveries of cancers in other groups of workers. Agran described the first comprehensive monograph written in the United States as follows:

> "After this four-year research effort - the German-born Hueper later described it as looking for 'one piece of dirt leading to another' - he had amassed the evidence necessary to write a monumental 896-page tome entitled *Occupational Tumors and Allied Diseases*. Published in 1942, the book, like Hoffman's earlier work, documented the existence of a series of high-risk occupations for cancer. But Hueper went further; he identified the suspected or recognized cancer-causing agents (carcinogens) associated with certain occupational cancer epidemics, and he argued for a cancer prevention strategy consisting of effective control measures to match the hazards of what he termed 'the new artificial environment.'
>
> Just as scientists learned in the nineteenth century that numerous pathogenic micro- and macro-organisms were the environmental agents of serious disease, so too, Hueper argued, the steady increase in the incidence of cancer since 1900 was due to the interaction of the human cells with a burgeoning variety of specific chemical and physical agents, some of them highly carcinogenic.

More than a statement on occupational cancer, Hueper's *Occupational Tumor* stands today as a singular contribution to the modern theory of environmental carcinogenesis. But, when it was published in 1942, the book failed to attract attention commensurate with its significance. The timing of its publication could hardly have been worse, coming as it did only weeks after the Japanese attack on Pearl Harbor. In Hueper's words, 'It was a difficult time to try to interest people in the loss of life.'

Among the multiple carcinogens which Hueper identified in *Occupational Tumors* were benzidine, beta-naphthylamine, and several other aromatic amines used in a wide variety of industrial processes and associated with a major increase in bladder cancer, most notably among exposed dyestuffs workers. In 1974, 32 years after the publication of Hueper's text, the newly established federal Occupational Safety and Health Administration (OSHA) was prompted to adopt national standards intended to limit worker exposure to 14 carcinogens. Among the 14 were benzidine, beta-naphthylamine, and other aromatic amines - the very same substances which Hueper had documented more than three decades before as potent occupational carcinogens. What were the institutional forces responsible for this tragic hiatus? Hueper's career provides some instructive insights into the barriers to effective preventive policies." pages 133-135, (7701)

Hueper's monograph described above is a highlight publication (4207); the book was follwed by a Public Health Report on *Environmental and Occupational Cancer.* Hueper defined environmental carcinogens as follows:

"Any physical, chemical, or parasitic agent forming a part of our natural or artificial environment that, on proper exposure, directly or indirectly elicits cancerous growths in one, several or all types of human tissues, represents an environmental carcinogen. Although some of these agents, like solar rays, soot, and arsenic, have a practically universal distribution, the occurrence of demonstrable environmental cancers is restricted, as a rule, to regions or to groups of individuals having a particularly intense, prolonged, or otherwise positive contact with these carcinogenic agents. Exposure to these factors is related to a great number of highly diverse environmental conditions, such

> as occupational activities, diets, medicines and medicinal devices, cosmetics, wearing apparel, building materials, habits and customs, climate, fauna, contaminants in drinking water, atmospheric air, foodstuffs, and - in recent years - procedures of warfare." pages 4-5, (4804)

The third monograph by Hueper was entitled *A methodology for Environmental and Occupational Cancer Surveys* which carried Hueper's affiliation as Chief, Cancerigenic Studies Section, National Cancer Institute (4210). Hueper also contributed to periodicals on the subject of industrial cancer and its control (4340) (4637) (4638) (4943) (4944). There was no mention of cigarette smoking in any of Hueper's monographs and periodical reviews appearing during the 1940's.

Willis, in his monograph entitled *Pathology of Tumors* (**highlight publication**) wrote a brief survey on occupation and cancer:

> "The association of particular kinds of tumours with certain occupations is sometimes too obvious to require statistical analysis, e.g. chimney-sweep's cancer, cotton-spinner's cancer, 'aniline' cancer of the bladder, carcinoma of the lung in the miners of Schneeberg and Joachimsthal, and osteosarcomas in the dial-painters of New Jersey. However, apart from immediately obvious occupational associations of this kind, statistical analysis shows significant occupational differences in the incidence of particular tumours or of 'cancer' generally. Thus the Registrar-General's report on cancer deaths in England and Wales for 1930-1932, showed general rates much higher than the average for furriers, glass-blowers, tin and copper miners, stevedores, curers, leather-dressers, etc., and rates much lower than the average for teachers, clergymen, retailers, telephonists, etc. Or, as an example of occupational differences of a particular kind of tumours, the mortality rates from cancer of the buccal cavity and pharynx were much higher than the average in barmen, furnacemen, dock labourers, horse drivers, general labourers, hotel keepers, etc., and much lower than the average in retailers, clergymen, tram drivers,

> railway officials, agents and brokers, teachers, bank officials, civil servants, farmers, etc. Although these differences are statistically significant, the occupational factor responsible for them are uncertain; occupations are often difficult to classify with precision, people change their occupations, and as regards tumour causation occupation earlier in life is more important than that engaged in later and recorded on a death certificate. However, the many occupational differences revealed by analyses such as the Registrar-General's afford hints of possible carcinogenic factors which are worth further statistical and experimental investigation. It is important to emphasize here the great length of the latent period often intervening between the application of the carcinogenic stimulus and the eventual appearance of the tumour. This makes it useless to look for the causes of human tumours in the occupations and habits of affected persons during the parts of their lives immediately preceding the appearance of their tumours. The tumour of today is often the consequence of stimuli applied 10, 20 or 40 years ago. Our medical histories, and therefore our statistical data, of tumour patients are often totally deficient in this respect; detailed inquiry into the occupations and habits of the whole of the patient's previous life, remote as well as recent, is rarely undertaken. Here is a great almost virgin field of research, exploration of which by competent workers with a full knowledge of the problems involved must be undertaken if we are to sift out of our complex environment the carcinogenic factors which are yet unrecognized. And the same applies to the elucidation of the causes of many other chronic diseases - blood dyscrasias, hepatic degeneration and cirrhoses, endocrine disorders, and chronic renal and arterial disease." page 87, (4802)

Willis was paraphrasing contents of his own article and those by British epidemiologists such as Heady (4939).

Tabulated Opinions on Occupational/Environmental Factors

The grouping of articles initiated for the 1930's (Chapter III, page 267) is being followed presently for the purpose of answering the following question: Outside of monographs and

reviews, how did medical authors relate occupational/environmental factors to cigarette smoking in discussion of pulmonary carcinogenesis? Did the article belong to any of the following: Group (a) Health hazards of occupational/environmental factors reviewed but no mention of cigarette smoking (4 publications); Group (b) Health hazards of occupational/ environmental factors with tobacco smoking mentioned but no opinion on preferential cause (19 publications); Group (c) Questions health hazards of occupational/environmental factors with no mention of tobacco smoking (1 publication); and Group (d) Questions health hazards of occupational/environmental factors with mention of tobacco smoking (2 publications).

Group (a) Articles on health hazards of occupational/ environmental factors with no mention of tobacco smoke.

(4023) Biederman; New York, NY

> "The industrial activities are definitely placed as causative factors. In the Schneeberg district, Bergkrankheit has been recognized as an industrial disease which has been shown to be cancer of the lung. A large proportion of the mining workers die of this 'chronic pulmonary disease.' **Insufficient protection against dust allows sharp particles to be inhaled and these irritate the bronchial membranes.** Kennaway and Kennaway by studying statistics on death certificates found that road workers, metal grinders and employees in gas works were most frequently involved." page 420, (4023)

(4087) Singer; Cedars of Lebanon Hospital, Los Angeles, CA

> "Occupation. - The occupation of patients who have carcinoma becomes important, particularly when carcinoma apparently follows some traumatic injury; **especially for those persons who work where there is a hazard of trauma, particularly in coal mines, in an atmosphere of**

silica dust, or where inhalation of tar fumes is likely. In the well-known mining district of Schneeberg many cases of carcinoma have developed in the workers. There many investigators attribute the carcinoma to the inhalation of arsenic and cobalt, while others feel that it may be due to the inhalation of silica dust." page 913, (4087)

(4784) Simonds & Anderson; Omaha, NE

"To explain the etiology of lung cancer many theories have been suggested, particularly in connection with the observation that the incidence is increasing. The relationship of chronic inflammatory changes following influenza or the inhalation of certain dusts and gases has been suggested. None of these factors have been proved to have definite etiology in lung cancer. The only carcinoma of the lung which can be correlated clinically with a known cause is the Schneeberg lung cancer developing in miners in certain regions of Saxony. A combination of arsenic and radium emanation in the dust of the mines and the local mechanical irritation of inhaled sharp dust particles seem to be etiological factors in this type of lung cancer." page 311, (4784)

(4962) Ryan & Myer, U.S. Naval Hospital (? location)

"The etiology of bronchogenic carcinoma has been the subject of much study and, except for a few instances where working conditions have been shown to have a very definite influence as a causative factor, no definite cause is known." page 863, (4962)

Group (b) Articles on health hazards of occupational/ environmental factors with tobacco smoking mentioned but no opinion on preferential cause.

(4049) Higgins; Medical College of Virginia, Richmond, VA

"To what extent tar particles contribute to the increase in pulmonary cancer is highly debatable. It is known that tar both clinically and experimentally is a potentially carcinogenic substance and in some countries its use on the roads has been followed by an increase in pulmonary neoplasm. Goltz has contrasted the annual application of half a million tons of tar on the roads of the United States with the fact that in Hong Kong

none of it is used and cancer of the lung is a rarity. This comparison, however, does not hold in every country and the case against tar is, therefore, not settled. **Closely linked with the possible role of tar is the evidence against tobacco.** The recent sale of a cigarette holder which encloses a cigarette through which the smoke is filtered is a graphic demonstration of the amount of tar resin introduced into the bronchial passages in the course of a day. The incidence of smokers in some series is remarkably high although Vinson noted the fact that only seventy of 140 cases of carcinoma of the tracheo-bronchial tree, at the Mayo Clinic, were smokers. Tobacco smoke as a lung irritant may be considered at least a possible cause of pulmonary malignancy in susceptible individuals but not necessarily a major factor. In any event, all known etiologic agents have in common the one characteristic of producing pulmonary irritation and, since they are so diverse, the only conclusion possible is that such irritation is the real activating or causative factor in the disease. Simonds asserts that the reduction of all the present known facts to one formula is a positive result of the work so far performed." page 363, (4049)

(4095) Tripoli & Holland; Charity Hospital, New Orleans, LA

"The etiology of carcinoma of the lung is still not clear. The factors most frequently emphasized include dust, chemicals, gases, fumes and tobacco, as well as such pre-existing diseases as influenza, tuberculosis, and syphilis." page 560, (4095)

(4096) Coleman; Columbia, SC

"The increased incidence of cancer of the lung is both relative and real. The wider use of coal tar products exhaust gases from automobiles, tobacco smoking, and other agents resulting in chronic pulmonary irritation are considered to account for the real increase in cancer of the lung." page 46, (4096)

(4156) Menne & Anderson; University of Oregon, Portland, OR

"Contamination of the air in areas of congested traffic and industry is receiving increased attention. Rosedale and McKay, and Dressler and Weigl incriminated chromate dust as provocative in chemical industrial workers. Continued emphasis is being placed on the role of coal dust, chemical agents, radioactive substances and silicosis in mining and other industries. More

recently investigators have turned their attention to the possible influence of the increased use of smoking tobacco (especially the marked increase in the use of cigarets)." page 2218, (4156)

(4209) Hadfeld & Garrod; St. Bartholomew's Hospital, London, GBR

"With the increasing tendency to regard cancer as the product of long-continued irritation, it is inevitable that attention should be directed to inhaled irritants. Gassing during the war and its sequelae apparently do not predispose to cancer, nor is there any good reason for incriminating tobacco smoke. There is no statistical evidence to indicate that exhaust gases from petrol engines are carcinogenic, but a study of occupational distribution extensive and detailed enough to yield significant data bearing on this point has yet to be made. Brockbank, who attempted such a study, found that the occupational labels found in ordinary clinical records were altogether inadequate for deciding whether there had been any unusual exposure to dust or fumes; a detailed personal interrogation could alone decide this. Since the exhaust of an internal combustion engine contains both lubricating oil and soot, substances both of which are carcinogenic in certain forms, the effect of modern traffic on city atmospheres is naturally regarded with suspicion, although Campbell reports negative results from exposing mice to an atmosphere polluted with the exhaust of a petrol engine. He has, however, observed an increased frequency in lung tumours among mice exposed to an atmosphere containing dust from tarred roads, and this effect was not altogether prevented by previous extraction of the tar in the dust with benzene." page 223, (4209)

(4233) Harrison; Shreveport, LA

"The inhalation of dust, motor fumes and tar fumes have been given considerable consideration. Automobile fumes and tar fumes have both been considered very seriously because the increase in the incidence of bronchogenic carcinoma has run almost parallel with the development of the automobile and the consequent use of tar in the roads. To date there has been no satisfactory evidence presented to support the case of street dust as the case of lung cancer. Tar does have a little more support. Moller painted the backs of young rats with tar and obtained the cornified squamous epithelial variety of lung carcinoma in all animals that survived the 300 days of painting. However, another investigator

exposed mice to an atmosphere containing much tar and no carcinoma was found. Carcinoma is common in Russia, where almost no tar is used. The importance of automobile gas fumes has been discussed but it is significant that the occurrence of the lesion is no more common among garage mechanics and truck drivers than in the general population. War gases have been mentioned but their importance seems to be slight. The same is true of tobacco smoke. It may be an irritant but it probably is not an important factor. If tobacco were the case of lung cancer, why has not carcinoma of the lips and tongue increased at a rate parallel with carcinoma of the lung." pages 2781-2782, (4233)

(4267) Wogelin; Pathological Institute, Berne, SWI

"Given the known carcinogenic action of tar, it is understandable that this substance should be given special attention in the case of lung cancer as well. However, it has been observed in animal experiments that lung cancers are often observed in mice whose skin had been painted with tar and in certain mouse strains with special predisposition to lung tumors, the number of lung cancers may increase enormously. In humans, an analogous case was reported by Mullschitzky, concerning a tar worker who contracted cancer of the scrotum 15 years earlier, cancer of the penis two years later and then keratomas on the face and wrists, and cancer of the earlobe, finally dying of the primary bronchial cancer. Transfer of the tar substances in the blood and excretion via the lungs is the most likely explanation for the localization of the cancer if the respiratory tract, since even intravenous injection of carcinogenic hydrocarbons results in lung tumors in mice. However, direct injury from inhaled tar particles is most likely in the case of human lung cancer, and tar spraying of the roads in indicated for this. Probst, however, showed that the increase in lung cancers began in Zurich even before tar spraying was used on streets and roads. In Denmark, Husted and Biilmann also failed to find any correlation with street tar spraying, and the increase in lung cancer is noted even in countries where street tar spraying has been performed only to a limited degree, such as, for example, in Russia. Following the experimental inhalation of road dust, Campbell observed lung cancer in mice, and the percentage was higher for tar-containing dust than for dust purified of tar. Intratracheal and intra-pulmonary injection of dibenzanthracene and other carcinogens yielded positive results in some cases and negative results in others. Accordingly, a role in the

induction of lung cancer cannot definitely be ascribed to tar, although it is possible that it is active in combination with other factors. The effect of smoking may be similar now that Schurch and Winterstein, as well as Roffo have induced skin cancer by the use of tobacco tar." pages 37-38 of English translation, (4267)

(4319) Amberson; NIH and Baltimore City Hospital, MD

"The cause of cancer of the lung is no better understood than that of other cancers. Suspected but unproved factors include preexisting chronic inflammatory lesions and the prolonged inhalation of irritating dust. The evidence is somewhat more convincing that the prolonged inhalation of dust of radio-active ores predisposes to cancer. **Recently a number of writers have indicted tobacco smoke and the fumes of automobile exhausts."** page 329, (4319)

(4336) Harnett; British Empire Cancer Campaign

"Kennaway classified the occupations of 18,280 persons dying from carcinoma of the respiratory tract for the years 1921-32. He found that in all occupations where there is exposure to road dust (pavers, road sweepers, horse and motor drivers) there is a high incidence of carcinoma of the lung. Most dusty occupations show no great frequency, with the exception of metal grinders, who are liable to fibrosis of the lung from silica dust, and in them the frequency of lung carcinoma is 2-1/4 times normal. Available data suggest coal tar, whether from road, chimney, or any other source, does not cause carcinoma of the lung; it is noteworthy that cotton mule spinners have an especially small liability, though they inhale air sprayed with carcinogenic oil. ... In occupations involving much inhalation of dust, there were 4 coal miners, 4 grinders, 3 chimney sweeps and 2 horse transport drivers. Agricultural work was represented by 7 gardeners and 6 farmers or farm labourers, and workers in gasworks by 5. In the absence of control figures of the occupations of all patients attending London hospitals, it is impossible to say whether these figures show any significant deviation from the average. **80 per cent. of the patients were town dwellers and 18 per cent. lived in the country. ... The percentage of smokers was estimated in group of 69 men and 18 women, mostly from one hospital.** Of the men 4.3 per cent. were non-smokers, 26.1 per cent. moderate, and 40.5 per cent. excessive smokers (over 3 oz. of tobacco per week), with 29 per cent. not

stated. Of the women, one-third were non-smokers, one-third not stated, and the remaining third were moderate smokers." pages 35-36, (4336)

(4350) McNamara; Dubuque, IA

"The rise in the incidence of the bronchogenic lung cancer has been concomitant with the development of the machine age, with the universal use of the gasoline engine, the urbanization of a great proportion of our population, and the prolongation of life through the effective control of many diseases. Therefore, it is evident that more people are exposed to more types of bronchial irritants over longer periods of time than ever before. Because of these facts it is not altogether surprising that bronchogenic carcinoma has increased so notably. Ochsner and DeBakey are convinced that the increased incidence of pulmonary carcinoma is due largely to the increase of smoking, particularly cigaret smoking, which is universally associated with inhalation. All of their patients with the exception of two women were heavy smokers. They published an interesting graph showing the parallel between tobacco production and the incidence of lung cancer per 100,000 population in the country. From the foregoing cursory review it is evident that many theories are held regarding the etiologic factors concerned in the development of bronchial carcinoma. Undoubtedly in most cases there is a combination of factors, including that of heredity." pages 225-226, (4350)

(4353) Murray; Brooklyn, NY

"Aside from the knowledge that some form of chronic irritation plays a leading role in the etiology of these tumors nothing really definite is known. Much speculation has been indulged in but nothing actually proven. Simons reviewed exhaustively all possible etiological factors, pointing out that some form of chronic irritation underlay practically all of them. With slight rearrangement these etiological factors are as follows: 1) Chemical - Inhalation of (a) tar particles, (b) motor exhaust fumes, (c) war gases, (d) tobacco smoke, (e) certain dust (as in pneumoconiosis or in the case of the Schneeberg miners). It is assumed that there has been a marked increase in the above during the past 30 years, coincident with the increase in the incidence of bronchogenic carcinoma." page 391, (4353)

2062855656

(4425) Clagett & Brindley; Mayo Clinic, Rochester, MN

"It has been stated many times that the inhalation of radioactive substances will cause the development of carcinoma of the lung. This fact has been demonstrated conclusively by the high incidence of bronchogenic carcinoma in the workers at the Schneeberg radium mines. ... The inhalation or irritating gases, such as exhaust gas from combustion motors and gases arising from tarred roads, has been proposed as a possible cause of pulmonary carcinoma. Many experiments seem to substantiate this belief. However, the incidence of bronchogenic carcinoma reported in those regions where the roads have not changed nor the number of cars increased has increased definitely. After a thorough study of the situation, most investigators of the subject have concluded that the inhalation of tar and benzene products is of little significance in the production of pulmonary carcinoma. ... **The opinion frequently has been expressed that the increase in bronchogenic carcinoma may be due to the increase in smoking and the inhalation of smoke."** page 840, (4425)

(4533) Holinger, Hara & Hirsch; Hinsdale Sanat., Chicago, IL

"As in all other cancerous lesions in the body, no primary cause is known. Innumerable secondary factors have been suggested and scrutinized. In an exhaustive review of the literature Simons mentions no less than 14 different predisposing causes. These are discussed further by Loizaga. It is generally agreed that no single agent is the sole cause, but that a chronic irritant is an essential common factor. Certain occupations seem to predispose to cancer of the lung. ... **Exhaust gases from automobiles and tar on roads have been considered as etiologic factors. Two of our patients, husband and wife travelled extensively from one job to another by automobile. He was a road builder. Both died of bronchogenic carcinoma.** Without other corroborative evidence, this, too, must be considered a incidental finding. ... The inhalation of tobacco in smoking is considered by some as a factor causing cancer." (pages 6-7, (4533)

(4554) Muller & Miller; Philadelphia, PA

"Inhalation of light oil derivatives of coal tar and dusts containing silica have likewise been shown to be of etiologic significance in lung cancer. The high incidence of lung cancer in the male sex as compared to

that of the female sex has been attributed to the use of nicotine, but the recent increase in female smokers has not led to an increase in lung cancer in females." page 42, (4554)

(4615) Clerf & Herbert; Jefferson Hospital, Philadelphia, PA

"Many theories concerning the cause of cancer have been presented. Among these are the occurrence of previous bronchopulmonary disease particularly influenza and inhalation of dusts, exhaust gases from automobiles and particles of tar from road beds. While these may under certain circumstances be considered as predisposing factors there is too little evidence to warrant their serious consideration. Many writers believe that inhalation of tobacco smoke is a responsible factor. Since chronic irritation is generally accepted as a predisposing cause, there should be ample evidence to support the theory that inhalation of tobacco smoke, particularly from cigarettes, is a factor." page 168, (4615)

(4635) Horn; University of Maryland School of Medicine, MD

"The etiology of bronchogenic carcinoma remains obscure. Chronic irritation, bacterial, chemical or physical, persists as a likely or probable contributing factor, despite recent contradictory evidence in the literature. Winternitz predicted an increase in the appearance of the neoplasm following the influenza epidemic of 1918-19. Ewing was firmly convinced that bronchogenic carcinoma occurred more frequently associated with tuberculosis. Macklin and Macklin, in a critical review of the subject of chronic irritation causing carcinoma of the lung, submitted statistical evidence that this hypothesis is unproved and eliminated chronic bronchitis, bronchiectasis, asthma, emphysema, pulmonary abscess, influenza, tuberculosis, and pneumoia as predisposing factors. Inhalation of certain chemicals in the form of dust has become an important consideration in the etiology of lung cancer, particularly in the field of industrial medicine. Karr and Vorwald compiling observations made from roentgenologic, post mortem and experimental studies, concluded that inhaled dusts, except those containing known carcinogenic agents, cannot be considered as causative factors in the development of bronchogenic carcinoma. Holleg and Anguist in a study of 12 cases of carcinoma of the lung in the presence of pulmonary asbestosis reached the same conclusion. The use of tobacco and its

relation to lung cancer has been a favorite subject of investigation. Ochsner strongly affirms that the rise in bronchogenic carcinoma is caused by the increasing use of tobacco." pages 170-171, (4635)

(4847) Levitt; Harper Hospital, Detroit, MI

"Many investigators have endeavored to establish a connection between bronchogenic carcinoma and chronic irritation of the respiratory tract. **Tobacco smoke, air pollution from the exhaust of automobiles, dust raised from tarry roads, have all been suggested as possible causes, but as yet, none of these factors has proven to be the specific cause.** Many attempts have also been made to establish a relationship between the occupation and the incidence of carcinoma of the lung. In an exhaustive article on *Occupational Cancer*, Hueper claims, 'It appears that the inhalation of radioactive gases or radioactive dust causes cancer of the lung such as that sustained by miners in Schneeberg and Joachimsthal.' He further adds 'that cancer of the bronchi and lung have been traced to an industrial exposure to arsenicals, chromates, nickel, carbonyl, soot, tar, asbestos and radioactive substances." page 396, (4847)

(4933) Fulton; London, GBR

"There appears to be little difference between the risk run by those employed in indoor as compared with outdoor occupations. In the latter group, labourers and transport workers provide the largest numbers but these groups constitute in any case a fairly high percentage of the outdoor occupation group. Attention might be directed to the apparently high number of cases occurring among furnacemen as a small group, and also among painters. In both of these groups, possible inhalation effects must be considered. While the actual number of cases is too small to justify the drawing of conclusions, the figures point to a possible relationship and appear to warrant a more complete investigation of the incidence of the diseases in these two groups. ... **No attempt has been made in this group to analyze the cases in terms of the possible effect of tobacco."** pages 777-778, (4933)

(4938) Hayes; Saranac, Lake, NY

"Predisposing Causes. - **These are unknown, although excessive smoking of tobacco and, in certain industries, radioactive emanations have been blamed.** The increased

> incidence has been parallel in the last four decades to industrial development with its noxious chemicals and gases." page 895, ref. (4938)

Group (c) Articles questioning health hazards of occupational/environmental factors with no mention of tobacco smoke. There was one article that questioned the role of occupational factor in lung cancer patients. The same article also did not mention tobacco smoke. A strict characterization of such articles would essentially be those that favor host susceptibility factors discussed below under Topic E.

(4060) Maher & Saderman; U.S. Navy, PA

> "Bronchogenic carcinoma seems to be on the increase. Perhaps more and better diagnostic procedures make this increase more apparent than real. Occupation did not seem to be a factor in our group." page 552, (4060)

Group (d) Articles questioning health hazards of occupational/environmental factors with mention of tobacco smoke. Both articles were by Ochsner and his collaborators. They wrote ten additional articles favoring tobacco smoke as a cause of lung cancer (see above, page 462).

(4164) Ochsner & DeBakey; Ochsner Clinic, New Orleans, LA

> "The inhalation of irritating gases, such as war gas, exhaust gas of combustion motors and gases arising from tarred roads, has been suggested as an etiologic factor in the production of pulmonary carcinoma. Kawahata observed 21 cases of carcinoma of the lung in six years among workmen employed in an illuminating gas generator and consequently exposed to dust and hot gases containing tar. Experimentally, it is possible to produce carcinoma of the lung in animals by the use of tar applied to the surface of the anima. Moller painted the backs of young rabbits with tar and observed that a fairly high percentage of the animals had bronchogenic carcinoma. Similar results were observed by Murphy and

Sturm. Seelig and Benignus found that, whereas only 1 of their control animals had carcinoma of the lung, 8 of 100 mice exposed to coal soot had such lesions. Kumura by means of intrabronchial inhalation of coal tar produced in the lung of a rabbit and a guinea pig small circumscribed nodular neoplasms. Smith observed no pulmonary tumors in 20 mice exposed to coal tar fumes, 1 carcinoma in 26 mice exposed to exhaust of an automobile and 1 pulmonary neoplasm in 29 mice painted with gasoline. He concluded that this proportion was not markedly greater than the spontaneous occurrence of carcinoma of the lung in such animals. Bonne performed experiments on mice by injecting intratracheally dried pulverized tar-acacia emulsion and found no significant increase in pulmonary tumors over control animals. Similarly, Campbell concluded that exposure of mice to exhaust gas from internal combustion engines has little effect on the incidence of primary tumors of the lung as compared with that among controls. Hampeln stated the belief that there is a definite relation to the increased production of smoke and dust in large cities, in that these substances by constant inhalations produce a chronic irritation of the bronchial and pulmonary epithelium, increasing the frequency of carcinoma of the lung. Staehelin also stated the opinion that the belief that the small tar and dust particles in the dust of tarred or oiled roads and the oxidation of products of gasoline and benzene inhaled daily in large amounts are causative factors for the increase. An increased incidence in carcinoma of the lung among open air workers exposed to road dusts was observed by Kennaway and Kennaway. Heilman also stated the opinion that the inhalation of gasoline and tar products originating from the use of automobiles and tarred roads is responsible for the production of pulmonary carcinoma. On the other hand, Davidoff and Uspensky stated that in Russia, where there are few automobiles and few, if any, of the roads are painted with tar, there has been a definite increase in carcinoma of the lung in the past ten years. Similar observations have been made by Boyd in Canada and by Husted and Biilman inn Denmark. Passey and Holmes contended that in Great Britain the increasing incidence in pulmonary malignant tumor began before the tarring of roads. Similarly, Konrad and Franke observed that the condition is increasing in the town of Riga, where there has been no increase in the tarring of roads or in the number of motor cars. As a result of his investigations of the tar content of dust raised from tarred streets by motor vehicles, Lehmann concluded that this factor is of little etiologic significance.

Probst made a thorough review of this subject and came to a similar conclusion. **These facts would certainly tend to disprove the importance of the inhalation of tar and benzene products in the production of pulmonary carcinoma."** pages 216-217, (4164)

(4555) Ochsner, Dixon & DeBakey; Ochsner Clinic, New Orleans, LA

"An apparently plausible theory concerning the cause of bronchiogenic carcinoma is inhalation of irritating gases such as exhaust gas of combustion motors and gases emanating from tarred roads. Kawahata observed 21 cases of carcinoma of the lung in six years among workmen employed in an illuminating gas generator and consequently exposed to dust and hot gases containing tar. Hampeln stated the belief that there is a definite relation to the increased production of smoke and dust in large cities in that these substances by constant inhalation produce a chronic irritation of the bronchial and pulmonary epithelium, increasing the frequency of carcinoma of the lung. Staehelin also stated the opinion that the inhalation of dust containing chemical substances which possess a specific carcinogenic agent is responsible for pulmonary carcinoma. An increased incidence of carcinoma of the lung among open air workers exposed to road dusts was observed by Kennaway and Kennaway. **This is not substantiated by our experience because in our 58 patients subjected to pneumonectomy, 32 (55.2%) had indoor occupations and 26 (44.8%) worked out of doors."** pages 1197-1198, (4555)

As stated above (page 468), DeBakey and his collaborators reversed their opinion on the primary importance of cigarette smoking as a cause of lung cancer. However, they did not alter their opinion on the questionable role of occupational/ environmental factors prior to 1950.

Human Studies on Industrial Pollutants

This subsection is devoted entirely to results of original studies on population groups for cancer incidence of lung, skin and liver. It is important to separate concepts evolving from

human studies and animal experiments. Among original studies listed below, the most important one that was repeatedly discussed through the 1950's and 1960's was entitled *Health Costs of Urban Air Pollution* by Mills and Mills-Porter (4862) and is selected as a highlight publication. Their articles listed below appeared prior to 1950; during the 1950's, both authors discussed additional role of cigarette smoking (see Chapter V). Harris did not mention articles listed during the 1940's and cited only those for the 1950's in his SOA report.

Mills wrote a historical review of the importance of urban pollution:

> "The industrial Revolution and modern machinery have wrought great changes in human existence. Many of these changes have been toward a higher type of life, but such blessings have not been un-mixed with evil. Growth of large metropolitan centers of great population density, and the use of enormous tonnages of coal for heat and power, have created certain hazards to health the true seriousness of which are finally coming to be realized. Quite aside from the social and economic aspects of city slums, the pollution of their atmosphere poses health problems quite as serious as those which were relieved by water purification plants a half century ago. Close analysis of the health damage wrought by such air pollution provides an ample basis for smoke clearance campaigns entirely aside from any probable reduction in laundry bills, painting and redecorating costs, etc. The average person takes two to three quarts of food and drink in through his mouth each day, but in the same time he takes into his lungs 10 to 20 thousand quarts of whatever atmosphere happens to be around him. Most of the dirt or pollution in this large volume of inspired air is caught and held in his respiratory system. Early in the present century Ascher pointed out the increased respiratory disease hazards faced by people living in atmospheres polluted by coal smoke. He found the pneumonia mortality 135 per cent higher in men of the Ruhr valley than in Prussian men of similar age groups, with the death rate highest in the

> industrialized areas of worst pollution. Pneumonia caused 6 times more nursling deaths in industrial than in rural populations. Ascher also found that coal smoke quickened tuberculosis deaths in laboratory animals and increased their susceptibility to aspergillus pneumonia. The damaging effect on people was greatest in those industrial areas where humidity was high and fogs prevalent. In 1912 White and Marcy presented data showing a close relationship between sootfall and pneumonia death rates in the 27 wards of Pittsburgh; with tuberculosis the relationship was less regular but still significant. They used only total mortality data, making no breakdown by sex or color. In 1938 Haythorn and Meller found that it concerned Pittsburgh men much more than women, for the male death rate from pneumonia was 50 to 90 per cent higher than the female in each year studied (1927-1936). They offered no explanation for this higher male rate. Necropsy findings of more marked anthracosis in lungs where healing had been by organization of unresolved pneumonia was suggested by them as probably due to a clogging of lung lymphatics with carbon particles." page 496, (4551)

Urban air pollution. Mills & Mills-Porter from the Laboratories for Experimental Medicine of the University of Cincinnati, wrote an article on this subject. In a study of death rates due to respiratory disease, Mills reported that incidence for respiratory tract cancer was higher in "dirtier industrial areas of Cincinnati and Pittsburgh, than in cleaner residential suburbs." The high rates for pneumonia and tuberculosis in slum areas have been attributed by other investigators to poor housing, overcrowding and poor nutrition. However, since male death rates were higher than women, Mills raised some doubt that these economic factors provided the whole answer.

In a later study, Mills & Mills-Porter added surveys for Chicago, Detroit, Nashville and Atlanta, and resurveyed Cincinnati (4862). Their conclusions were as follows:

"Death rates for pneumonia, pulmonary tuberculosis and respiratory tract cancer bear a direct and significant relationship to the intensity of pollution in urban atmospheres. Males are involved much more than females in these effects of pollution. In Chicago, where large population numbers give stable results, the rise in death rates from pneumonia and tuberculosis from clean to dirty districts is ten times greater for males than for females, and the rise in death rates for buccal and respiratory tract cancer is more than four times greater. Based on the low rates prevailing in its clean suburbs, Chicago each year has an excess of 258 deaths from pneumonia among white males in its dirtier districts, 241 from tuberculosis and 69 from buccal and respiratory tract cancers - a total of 568 deaths among white males each year from these three respiratory diseases alone in excess of the death rates these diseases show in the city's cleanest districts. Add to this one-tenth as many deaths for white females and for Negro males, and a grand total is obtained of roughly 700 deaths each year, which represents a measure of the respiratory hazard of living in Chicago's dirtier districts. **The observation that death rates from buccal and respiratory tract cancers rise along with those from pneumonia and tuberculosis points strongly to a general irritation of thee tract as the basic factor involved. Economic, housing and nutritional factors appear of much less importance than air pollution, as evidenced by the difference between hazards to males and females."** page 633, **(4862)**

Mills and Mills-Porter further discussed the potential role of cigarette smoking:

"The tenfold difference in excess deaths between males and females in dirty districts seems much more than could be accounted for on the basis of more daily hours of exposure in the dirty air for the men. One would be inclined to look elsewhere for a factor which is working synergistically with the outdoor air pollution to affect the respiratory tracts of men in particular. One at once thinks of tobacco smoke in this connection for the percentage of men who smoke is almost three times as great as that of women. In an article soon to be published, we shall show that tobacco smoking is significantly related to buccal and respiratory tract cancer and pulmonary tuberculosis, while Morton recently reported postoperative pulmonary complications six times more prevalent in patients who were habitual smokers

> before operation than in nonsmokers. **It is therefore quite possible that the really alarming respiratory hazard men face in urban areas of heavy air pollution may be due to the combined and cumulative effects of such pollution in conjunction with the chronic irritational action of tobacco smoke.** In cleaner suburban or rural areas, the respiratory hazard is only slightly greater for men than for women; women (with a low percentage of tobacco smokers) are less affected by the air pollution hazard. Hence we must consider the likelihood that the male hazard results from the combined effects of coal smoke and tobacco smoke." page 631, **(4862)**

The authors proceeded to discuss outdoor air pollution that continue to apply through the 1980's when a new Clean Air Act is under consideration:

> "The needed steps for lessening outdoor urban air pollution have already been discussed. Widespread change to diesel power for railroad switching and long haul purposes has brought great improvement except in cities near the sources of high volatile coal, such as Cincinnati, Birmingham, Ala., Nashville, Tenn., and Louisville, Ky. These cities will get relief only through compulsory dieselization. Compulsory use of low volatile coal in hand-fired heating equipment has been shown to provide the best solution to smoke production in the home, but the increased demand for the limited supplies of low volatile coal bid fair to bring about a considerable price boost. Methods of processing high volatile coals for smokeless combustion are now receiving intensive study, so great relief from the carbon factor in air pollution may be expected. Fly ash and industrial dusts or wastes still pose a difficult problem, however, one on which St. Louis is now busily concentrating her attention after her remarkable victory over the carbon and sulfur oxide factors." page 632, **(4862)**

Incidence of lung cancer in six cities. Dorn, a senior economist at the U.S. Public Health Service, examined the number of new cases reported in 1938 to 1940 from six cities: Philadelphia, Alameda and San Francisco, Chicago, Detroit,

Pittsburgh and Denver. Dorn discussed the role of air pollution as follows:

> "Although exact measures of the air pollution are not available, it is generally thought that, of the cities listed in table 4, the greatest amount of pollution is in Pittsburgh. However, the incidence rate for lung and respiratory cancer in males is lower in Pittsburgh than in any of the other cities except Denver. There is less difference in the rates for females; in fact these data indicate that there is no real difference in the rates of the surveyed cities. These data do not necessarily prove that atmospheric pollution has no effect upon the incidence of respiratory cancer. On the other hand they offer no affirmative evidence that such is the case. The causes of respiratory cancer are probably too complicated to be discovered in this relatively crude manner." pages 1270-1271, (4330)

Occupation and incidence of lung cancer. Kennaway & Kennaway (4759) extended the statistical analysis of death certificates for lung cancer in males from England and Wales. Their earlier publication covered deaths reported from 1921 to 1932 (see Chapter III, page 265) and their later one that extended coverage to 1938, is selected as a highlight publication. The conclusions of the Kennaways apply only to England and not to the United States, because of differences in fossil fuel consumption:

> "(1) The death certificates for cancer of the lung and of the larynx in males from England and Wales for the years 1921-38 inclusive numbering 38,418 have been investigated and the periods 1921-32, 1933-38 are compared. The 63 occupations examined employ about 30 per cent of the male population aged 20 and upwards. (2) Sources of error in statistical work on death certificates are discussed. (3) The increase in the recorded cases of lung cancer cannot be attributed to any increase of data obtained by autopsy. (4) The agricultural and coal-mining industries show a low

incidence of cancer of the lung and of the larynx. (5) A group of open-air occupations where there is exposure to the dust of roads has ratios above 100 for cancer of the lung and of the larynx with the exception that motor drivers have a normal liability to cancer of the larynx. But the comparative incidence of cancer of the lung is not increasing distinctly in any of these occupations and in the pavers, street masons, concretors and asphalters there has been a distinct fall in the ratio. (6) The occupations in which there is a liability to silicosis do not show a high incidence of cancer of the lung, but there are in the literature some studies of small numbers of cases in which the two conditions were asso-ciated. (7) Cases of cancer of the lung have occurred in some occupations involving exposure to asbestos. (8) In the death certificates examined and in the Reports of the Chief Inspector of Factories, no occupations involv-ing exposure to any kind of dust except those concerned with asbestos, arsenic and nickel which employ very small numbers have been found in which there might be an increased incidence of cancer of the lung. (9) **Workers exposed to coal gas and tar tend to show an increased prevalence of cancer of the lung but in the later period studied the incidence does not exceed two and a half times that on the general population.** (10) Occupations concerned with the supply of alcohol have a high incidence of cancer of the larynx. (11) The later period studied shows a consider-able decrease in the occurrence of cancer of the lung in those engaged in the preparation and sale of tobacco. (12) The very moderate ratio (125) for cancer of the lung in medical men is important in regard to the view that the recent rapid increase in recorded deaths from cancer of the lung is due to the detection of more cases by improved diagnosis, for this is an occupation where the availability of the existing methods for the detection of cancer is presumably at a maximum. (13) No special occupations have been found, among the 63 examined, to which the increase in the total of cases of cancer of the lung can be attributed. This increase is now so great that the incidence upon any such occupations would have to be very high indeed. (14) No evidence has been found that tarring of roads has affected the incidence of cancer of the lung. Such data as are available suggest that coal tar in the atmos-phere, whether derived from roads, domestic chimneys or any other source, does not cause an exceptionally high incidence of cancer of the lung. Cotton mule spinners show an especially high incidence of cancer of the lung, although they inhale air sprayed with an oil which

produces cancer of the skin. Much further work is required on the factors which regulate the penetration of particles and droplets of various shapes and sizes into the air passages. (15) **The higher mortality from cancer of the lung in towns,the low mortality in agricultural occupations, and the absence of social gradient are compatible with an etiological factor in the air such as coal smoke.** But in any comparison of urban and rural areas, the question of facilities for diagnosis must be considered. (16) Soot is probably a decreasing contaminant of the air owing to the substitution of other sources of heat for the domestic fire, which is the chief source of soot-containing smoke. Hence coal smoke does not account well for any recent increase in cancer of the lung. **Among various possible factors which have been suggested to account for the increase is tobacco smoke; the consumption of tobacco has risen, and so has the percentage of it smoked in the form of cigarettes of which the smoke is often inhaled: such an effect of tobacco would accord well with the absence of social gradient."** pages 296-297, (4759)

The role of tobacco smoke in lung cancer patients was discussed by the Kennaways:

A possible connection between tobacco, and especially cigarettes, and cancer of the lung, has been suggested many times, perhaps most recently in the case of Turkey. Peacock has pointed out that cancer of the stomach is far more common in man than, so far as we know, in any other species and has suggested that this is due to his use of heated foods. A similar argument might be applied in the case of cancer of the lung, which is not known to be prevalent in any of the lower animals. The adenoma of the lung of the mouse, and certain affections of the lung of sheep in South Africa and Iceland, are neoplasms of which the exact nature is uncertain. We know one instance at any rate of the susceptibility of the lung of an animal to a carcinogenic agent namely the lung of the cat in relation to 2-acetylaminoflourene given by the mouth: hence there is no reason to think that animals are immune to any such agents. One obvious factor, possibly carcinogenic, to which the lung of man alone is exposed is tobacco smoke. During the present century very considerable changes have taken place in this country in the social distribution of the various method of smoking. There were of course exceptions to any rule, but roughly one might say

that in the earlier part of this period men of the richer classes smoked pipes, cigarettes and cigars, and men of the poorer classes smoked pipes: cigarette smoking was increasing among the richer women, while women of the poorer classes did not smoke. One never saw a women scrubbing her front door-step or hanging out the washing, with a cigarette in her mouth. The great change which has taken place in the later years is the general increase of cigarette smoking and its adoption by women of classes which formerly did not smoke at all. Men in occupations which do not subject them to any restrictions in this matter, e.g. builders, workmen, painters, window cleaners, dustmen and road sweepers, who used to smoke a pipe at meal times, now smoke cigarettes while at work. Cigarette smokers are said to inhale more than do smokers of pipes, but it is very difficult to get any conclusive evidence upon this matter, which might be important. There is some American literature, which has been summarized upon the arsenic content of tobacco and tobacco smoke. The occurrence of cancer of the lung in makers of arsenical sheep-dip indicates the impossible importance of this factor. Some writers have contended that smoking cannot be associated with cancer of the lung because this form of cancer has increased more among men, while the use of tobacco has increased more among women. But the sexual distribution of cancer involves unknown factors and does not provide a very secure basis for an argument of this kind. Of course no claim is made here that the simultaneous increases in the consumption of tobacco, and in cancer of the lung, proves any etiological connection between the two. Other changes which have taken place in the same period, which no one proposes to associate with cancer of the lung, e.g. the increase in the issue of wireless licenses show a very similar curve, and such correlations are a common subject for statistical witticisms. Thus wireless licenses have increased at a rate (about 10-fold in the last 20 years) similar to that shown by deaths from cancer of the lung, or from coronary disease. The annual consumption of tobacco in the United Kingdom has increased from 128 million pounds in 1924 to 250 million pounds in 1946, and the percentage of these amounts smoked in the form of cigarettes has risen from 56 in 1924 to over 80 in 1943-5. Thus the consumption of cigarettes shows a considerable increase both absolute and relative." pages 293-295, (4759)

Additional publications on causation of lung cancer. Farber & Edwards, from the San Francisco Department of Public Health,

reviewed the medical history of 50 cases of primary lung carcinoma. They reported that in 16 individuals (32%) there was an exposure to dust or other irritating substances (4524). Moshman and Holland reviewed the age standardized rate of cancer among Oak Ridge employees and their resident dependents. The lung cancer rates in white males was proportionately higher than national average which could not be explained because of lack of information on personal habits and socio-economic conditions (4954). In an editorial entitled "Aetiology of Lung Cancer" appearing in the British Medical Journal, the following sentence appeared: "Tar, certain lubricating oils, soot, arsenic and various radioactive substances will cause epithelioma of the skin; the long continued inhalation of any such substance may well produce cancer of the lung." (4331). The editorial opinion emphasized the lack of inhalation studies relevant to lung cancer in contrast to numerous animal skin experiments relevant to human skin cancer.

Occupation and skin cancer. A monograph entitled *Cancer of the Scrotum in Relation to Occupation* was written by Henry, formerly H. M. Medical Inspector of Factories (4601). He also wrote a comprehensive review article entitled *Occupational Cutaneous Cancer Attributable to Certain Chemicals in Industry*. It is important to recognize that the chemicals in coal tar products were also being tested in animals and shown to cause skin cancer. Henry and his colleagues did not support the

suggestion that studies on coal tar applied to skin are relevant to pulmonary carcinogenesis associated with cigarette smoking. Other publications on skin lesions due to pitch and tar did not suggest that tobacco tar could likewise cause lung cancer (4727) (4781) (4879).

Experimental Dermal Carcinogenesis

During the 1940's, there was an intensive testing of polycyclic aromatic compounds on formation of skin cancer in experimental animals, preferentially mice. I have collected over 60 articles from scientists in the United States, Great Britain and other countries. It is important to emphasize that there were no statements relating to application of results of dermal carcinogenesis to cigarette smoking and lung cancer. The exceptions to this general rule are mentioned below and relate to the occurrence of benzpyrene in coal tar and tobacco tar.

Pathology of tumours. This was the title for the monograph written by Willis (from the Royal College of Surgeon, London) and a highlight publication for the 1940's. The chapter on *Experimental Production of Tumours* included the background for searching carcinogenic agents in tars and oils (4802):

> "Since tars and oils are highly complex mixtures of substances, and since different tars and oils were found to vary markedly in their carcinogenic efficacy, it soon became evident that a search must be made for specific ingredients responsible for carcinogenesis. Many workers cited by Woglom investigated the relative efficacy of tars of different kinds, of different tar-fractions obtained by distillation, and of tar extracts

made with solvents. Notable amongst these was J. A. Murray who prepared a highly carcinogenic ethereal extract of tar. But by far the most important of the researches into the chemistry of carcinogenic tars were those of Kennaway and his collaborators from 1923 onwards, the main results of which were outlined by Kennaway in 1930. These showed that the carcinogenic factor in tar was present in the higher-boiling fractions; that potent carcinogenic tars could be made artificially by heating acetylene, isoprene, skin, yeast, cholesterol or human skin or voluntary muscle to temperatures between 700° and 920°C.....; and that a non-carcinogenic petroleum could be made carcinogenic by heating to 800°C., in the process of which aromatic hydrocarbons are formed from those of the aliphatic series. Twort and Fulton prepared highly active tars by heating turpentine and pinene. In 1930 Mayneord and Hieger, working with Kennaway, made the important observation that the fluorescence spectra of many cancer producing mixtures, including gas-tar, acetylene-tar, yeast-tar, muscle-tar, cholesterol-tar, ethereal extract of gas-tar, pitch distillate, heated petroleum and shale oil, showed the same bands at wave-lengths 4,000, 4,180, 4,400 A. These bands were like those of the fluorescence spectrum of the polycyclic hydrocarbon 1:2-benzanthracene. Accordingly, Kennaway made a special study of hydrocarbons allied to 1:2-benzanthra-cene, and found 1:2:5:6-dibenzanthracene to be carcinogenic. **At last a chemically pure carcinogenic compound had been identified, not indeed as a constituent of tar, but as a result of painstaking studies of the physical and chemical characters of carcinogenic tars.** Kennaway was careful to point out that 'neither benzanthracene nor any of its derivatives have been found and perhaps have not been sought for, in coal tar', and to suggest prophetically that among the many compounds still undiscovered in tar some might be found 'far more powerfully carcinogenic than any known substances'. So also Hieger, in discussing the significance of the discovery of characteristic bands in the spectra of carcinogenic mixtures, insisted that 'the substance responsible for the bands may not be identical with the cancer-producer but is some closely allied compound ... The carcinogenic agent in tars and oils may be only one of a group of such compounds'. The value of the fluorescence test was, in Hieger's own words, 'to indicate the probability of carcinogenic activity and to assist in directing the preparation of appropriate hydrocarbons'." pages 31-33, **(4802)**

Willis summarized five groups of carcinogenic hydrocarbons that were tested in pure form on experimental mice, as follows:

> "The importance of the discovery of pure carcinogenic hydrocarbons by the London workers can scarcely be exaggerated. It gave a tremendous impetus to both chemical and biological work in this field. Many new carcinogenic compounds have been produced, and tar-cancer research has largely been superseded by more precise researches with these chemically pure substances. The number of such substances now runs into scores, and only the most important can be mentioned here. For more detailed accounts, consult the papers of Kennaway and his co-workers already cited, and those of Fieser and Shear.
>
> (a) Simple derivatives of 1:2-benzanthracene. This substance, 1:2-benzanthracene itself is only very feebly carcinogenic, but many of its simple substitution derivatives are much more active. This applies particularly to derivatives containing substitution groups at the position 10, 5, 9 and 6 of the benzanthracene complex. Thus 10-methyl-1:2-benzanthracene, 5-methyl-1:2-benzanthracene, 9-methyl-a:2-benzanthracene, and 6-methyl-a:2-benzanthracene have all been prepared synthetically and shown to be active carcinogens, in that order of decreasing potency. Further, if suitable simple substituents are introduced into two of these favourable positions, they then reinforce each other, giving a highly potent carcinogenic compound. This applies to the 5:6, 5:9, 5:10 and 9:10 dimethyl derivatives. The last-named is **the most active carcinogenic hydrocarbon** so far discovered; with it, Bradbury and co-workers obtained skin cancers in mice as early as the 32nd day after the initial application.
>
> (b) Methylcholanthrene and cholanthrene. These merits special interest, not only because the former is second only to 9:10-dimethyl-1:2-benzanthracene in carcinogenic activity, but also because **the cholanthrenes are closely related chemically to the bile acids.** Thus methyl-cholanthrene has been prepared from both deoxycholic acid and cholic acid; and both it and the parent hydrocarbon cholanthrene have also been synthesized. Ethylcholanthrene has also been prepared and shown to be an active carcinogen. From the structural formulae it will be seen that these compounds again are really 1:2-benzanthracene derivatives with substituents in the carcinogenically favourable positions 10, 5 and 6; methylcholanthrene being particularly notable in that all three of these positions carry substituents.

(c) 3:4-benzpyrene. This is certainly the most active and perhaps the only important, carcinogenic constituent of coal tar. It was first isolated from coal-tar pitch, and later prepared synthetically. In accord with Kennaway's 1924 work, the highest boiling fractions of tar contain relatively large amounts of benzpyrene; and the fluorescence spectrum of benzpyrene is of the same type as that of 1:2-benzanthracene. Its close relationship to this substance is evident from its structural formula, which shows that it is really a benzanthracene derivative with an additional benzene ring affecting position 9, where we have already seen substitution is favourable for the development of carcinogenic properties. Benzpyrene is only slightly inferior to methylcholanthrene in potency. Some of its simpler derivatives are also carcinogenic, though less powerfully so than the parent hydrocarbon. A high order of carcinogenic activity is shown also by three hexacyclic dibenzpyrene which have been prepared.

(d) 1:2:5:6-dibenzanthracene. This is notable as being the first pure hydrocarbon to be shown to be carcinogenic; and since the discovery of this substance, it has been widely used by research workers. It is capable of producing tumours in a high proportion of mice, but it does so relatively slowly. In molecular structure it also is a 1:2-benzanthracene derivative with an added benzene ring as a substituent at positions 5 and 6.

(e) Some other carcinogenic hydrocarbons and related compounds. Certain other hydrocarbons and certain heterocyclic nitrogen-containing compounds with structures analogous to the carcinogenic hydrocarbons of benzanthracene type have also been shown to be feebly carcinogenic. These include 1:2:5:6-dibenzfluorene, 1:2:5:6-dibenzacridine, 3:4:5:6-dibenzacridine, 1:2:5:6-dibenzcarbazole and 3:4:5:6-dibenzcarbazole. The ways in which these compounds resemble and differ from the benzanthracene derivatives in molecular structure are shown in Table I. Dibenzcarbazole also produces liver tumours in painted or injected mice. It is of interest to find that 3:4-benzphenanthrene and 2-methyl-3:4-benz-anthrene, which are unrelated to benzanthracene, have considerable carcinogenic potency. Morton et al also claimed that triphenylbenzene and tetraphenylmethane were carcinogenic, but Cook and Kennaway, Shear and others have been unable to confirm this. The discovery of Kennaway and co-workers, referred to by Badger et al., that under certain conditions deoxycholic acid, a normal component of bile,

can induce sarcomas in mice, is a remarkable one and may prove of far-reaching importance." pages 33-34, (4802)

Finally, Willis reviewed the relative potency of carcinogenic hydrocarbons. The order of potency from highest to lowest was as follows: 9:10-dimethyl derivative of benzanthracene, methylcholanthrene, benzpyrene, dibenzanthracene, and dibenzacridine.

National Cancer Institute. The scientists from this Institute supported by the U.S. government, and their field of research relating to dermal and pulmonary carcinogenesis following administration of polynuclear aromatic hydrocarbons, were as follows:

(4020) Andervont: susceptibility of hybrid mice to pulmonary tumors induced by subcutaneous injection of methylcholanthrene.

(4021) Andervont & Shimkin: pulmonary tumors in mice induced after intravenous or subcutaneous compounds such as 3:4-benzpyrene and 20-methylcholanthrene.

(4039) Grady & Stewart: pulmonary tumors induced in strain A mice by subcutaneous injection of 1,2,5,6-dibenzanthracene or methylcholanthrene.

(4040) Grady & Stewart: pulmonary tumors arising from alveolar cells began to appear 5 weeks after subcutaneous injection.

(4083) Shimkin: susceptibility of seven strains of mice to pulmonary tumors induced by intravenous injection of methylcholanthrene.

(4084) Shimkin: continuation of induction of pulmonary tumors in mice; the substances which have been found to produce pulmonary tumors in mice include tar, probably owing to its content of the three common polynuclear aromatic hydrocarbons: methylcholanthrene, dibenzanthracene and benzpyrene.

(4085) Shimkin & Andervont: relative potency based on latent time or carcinogenic index of methylcholanthrene, benzpyrene and dibenzanthracene.

(4086) Shimkin & Letter: The Discussion and Summary are important because they include significance of animal experiments to human lung cancer and air pollution. This article is the only highlight publication under the subtopic of experimental carcinogenesis of polynuclear aromatic hydrocarbons conducted by American scientists:

> "The incidence and the number of primary pulmonary tumors in mice of susceptible strains can be increased by the introduction into the animal of carcinogenic hydrocarbons and related compounds. The susceptibility of the mice to induced pulmonary tumors is parallel to their susceptibility to spontaneous tumors of the lung, i.e., strains which are most susceptible to their spontaneous occurrence are most susceptible to their induction with carcinogens. The carcinogenic chemicals can be injected by various routes, including the intra-tracheal, in order to elicit the neoplastic response in the lungs. **Experiments conducted at this laboratory suggest that the increase in the number of pulmonary tumors in mice exposed to certain dusts is not owing to nonspecific irritation but to the presence of some carcinogenic material in the dust.** Campbell obtained the highest incidence of pulmonary tumors in mice exposed to dust from tarred roads. It is known then some coal tars contain a powerful carcinogenic agent, 3,4-benzpyrene. The increase in the incidence reported with dust which had been extracted with benzene was not so impressive, and no indication concerning the

completeness of the extraction was given. Contrary to Campbell's postulation that nonspecific irritation plays a part in the genesis of pulmonary tumors in mice, the experiments reported here fail to indicate that nonspecific irritation produces pulmonary tumors in mice or aids in their induction with carcinogens. It is also significant that the development of pulmonary tumors in mice of strain A injected subcutaneously or intravenously with 1,2,5,6-dibenzanthracene or 20-methylcholanthrene is not associated with any demonstrable inflammatory reaction. One of the possibilities given in explanation of the increase in the pulmonary tumors in mice painted with tar is that the procedure in some ways alters the physical state of the animal so that its resistance to carcinogenesis is lowered, and pulmonary tumors arise at points of incidental irritation of inhaled dust particles. Mice born and raised in an atmosphere practically devoid of dust are just as susceptible to the induction of pulmonary tumors after the subcutaneous injection of 1,2,5,6-dibenzanthracene as are the animals maintained under normal conditions. The present report also supports the view that no external adjuncts, such as atmospheric dust, appear to be needed in the production of pulmonary tumors in mice with carcinogenic agents. Whether the action of carcinogens, such as 20-methylcholanthrene, is a general one, producing tumors secondary to some alteration in the whole organism, or whether its action is a local one upon the tissues at the site of application, remains one of the most important undetermined question. The present available evidence, however, points toward local action in the induction of pulmonary tumors. After the subcutaneous injection of 1,2,5,6-dibenzanthracene the absorption spectrum fails to reveal the presence of the compound in the lungs, although pulmonary tumors are induced. That the agent or some active derivative does reach the lungs, however, is suggested by the presence of photodynamic activity of emulsions of the lungs of mice injected subcutaneously with 3,4-benzpyrene.

The increase in the incidence of bronchogenic pulmonary carcinoma in man has attracted the attention of oncologists and public health officials. One of the theories presented is that the stimulus for its occurrence may be found in the atmospheric dust particles introduced into the lungs. Passey in 1922 demonstrated the presence of compounds carcinogenic to mice in the soot of soft coal discharged into the air. Campbell established that there was a marked increase in the incidence of primary pulmonary tumors in mice exposed to the dust of tarred roads. The presence of active

carcinogens in the atmospheric dust may be of public health significance and deserves systematic investigation and attention. This report indicates the biologic testing which may be applied for the project: (1) The subcutaneous injection into male mice of strain C_3H of benzene and other extracts of dusts gathered in various localities: and (2) the intravenous injection of the unextracted dusts into mice of strain A. It must be remembered, however, that experiments on mice should not be applied, except as leads for further investigations, to other species of animals, including man. Thus, 1,2, 5,6-dibenzanthracene in 0.1 mg. intratracheal doses induced pulmonary tumors in strain A mice, the introduction of much larger amounts into the trachea of rats failed to produce tumors of the lung in these animals. The only authoritative reports of the induction of pulmonary neoplasms in man by means of inhaled dust are those of the Schneeberg and Joachimstahl miners who were exposed to radioactive ores. Whether substances which are carcinogenic to mice are also carcinogenic to man, and in what doses and under what conditions, is a matter of conjecture. The pulmonary tumors in mice are similar to the pulmonary neoplasms of man in that both are found in the lungs. But, whereas the human neoplasm is believed to be almost exclusively a bronchogenic carcinoma, the mouse tumor is an adenoma or adenocarcinoma arising from the alveolar wall lining, and quite different in its development, site, and biology.

Summary. The single intravenous injection of 5 mg. of arsenopyrite, chromite, or thorite, or of 1 mg. of quartz ore (particle size 1.6 to 3.5 micra) did not induce primary pulmonary tumors in strain A mice within 6 months after the administration, despite the presence of chronic irritation. The intravenous injection of these ores did not increase the number of primary pulmonary tumors, nor did it apparently have any other effect upon the development of such tumors following the intravenous administration of 0.1 mg. of 20-methylcholanthrene. **Soot from a chimney burning soft coal contains a benzene-soluble compound capable of initiating subcutaneous sarcoma and primary pulmonary tumors in strain C_3H male mice.** The single intravenous injection of 2.5 mg. of the unextracted soot increased the incidence of primary pulmonary tumors in strain A mice." pages 251-253, **(4086)**

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(4119) Andervont: hepatic changes and pulmonary tumors after subcutaneous injection of 3,4,5,6-dibenzcarbazole in different strains of mice.

(4155) Lorenz & Shimkin: latent period following injection of methylcholanthene and appearance of pulmonary tumors.

> "Rate of disappearance of methylcholanthrene from lungs and body did not explain the marked difference in susceptibility of two strains of mice to induced pulmonary tumors. It therefore seems probable that pulmonary tumors arise long after the introduction of the stimulus and long after the removal of the stimulus from the body." page 497, (4155)

(4260) Shimkin & Lorenz: injection experiments suggest mode of action of pulmonary carcinogens, particularly of methylcholanthrene.

> "1. Intravenous injection of methylcholanthrene dispersions in which the particles are 10μ to 20μ in size induce at least 10 times as many pulmonary tumors in strain A mice as similar dispersions in which the particles measure 1μ to 2μ. The neoplastic reaction depends upon the actual amount of the hydrocarbon that lodges in the lungs and not upon the amount injected into the organism. **This is evidence supporting the view that the pulmonary tumor reaction is a local one of the hydrocarbon upon the susceptible pulmonary tissue rather than a general systemic effect.** 2. The lungs of young, small strain A mice are more susceptible to the induction of pulmonary tumors with intravenous dibenzanthracene than the lungs of old, large mice of the same strain. The amount of hydrocarbon retained in the lungs is the same in both cases, but the smaller lungs of the young mice permit a higher concentration of the hydrocarbon in the tissue." page 509, (4260)

(4323) Bryan & Shimkin: dose-response data obtained with three carcinogenic hydrocarbons in strain C_3H male mice.

(4414) Andervont: occurrence of mammary tumors in mice influenced by segregation.

(4964) Shimkin & McClelland: statistical analysis of data on the induction of pulmonary tumors in strain A mice following intravenous injection of methylcholanthrene.

(4968) Stewart: review research on carcinogenic agents in progress at the National Cancer Institute:

> "In summary, a few of the uses being made of carcinogenic agents in work now going on at the National Cancer Institute have been described. By means of these substances we hope to be able to identify the factor or factors which may be essential in the production of neoplasms, and also to determine what the earliest stages of cancer look like, so that neoplastic disease may be detectable in a curable stage. Finally, we hope some day to ascertain the underlying characteristics which are peculiar to cancer cells. This calls for the collaboration of all the medical sciences, as well as the disciplines of physics, biochemistry, radiology, nutrition and others. Only by such an all-out attack will the nature and origin of cancer be determined. It can be seen that the problem of tumor induction by carcinogenic agents touches the very core of the problems of growth and life." page 1096, (4968)

Cancer research laboratories in the United States. The research activities conducted at private institutions were less extensive than those at the National Cancer Institute. The following list includes research topics relating to environmental factors in dermal carcinogenesis.

(4054) Law; Jackson Memorial Laboratory, Bar Harbor, ME: amniotic fluid injection of 1:2:5:6-dibenzanthracene in mice.

(4092) Syverton & Berry; University of Rochester, NY: sarcomata and carcinomata induced by methylcholanthrene in cottontail rabbits.

(4230) Green; Bryn Mawr College, PA: crystalline material in lung tissue of mice after subcutaneous injection of 1:2:5:6-dibenzanthracene.

(4424) Carruthers & Santzeff; Washington University School of Medicine, St. Louis, MO: chemical studies on transformation of mouse epidermis by methylcholanthrene.

(4427) Cowdry & Suntzeff; Washington University, St. Louis, MO: tumors induced by methylcholanthrene appeared more quickly and in a higher percentage of young than in old mice.

(4437) Friedewald & Rous; Rockefeller Institute for Medical Research, New York, NY: benzpyrene brought about neoplastic changes in rabbit epidermis; there was no reference to publications by Roffo among 34 citations.

(4471) Silberberg & Silberberg; New York University College of Medicine, NY: benzpyrene applied to skin of mice accelerated wound healing.

(4471) Silberberg & Silberberg; New York University College of Medicine: benzpyrene effect was slower than that of benzene.

(4518) Cowdry; Washington University, St. Louis, MO: epidermal carcinogenesis after methylcholanthrene in mice.

(4572) Simpson & Cramer; Washington University, St. Louis, MO: methycholanthrene dissolved in lanolin was rendered inactive on mouse skin.

(4618) Dunlap & Warren; Harvard Medical School, MA: derivatives of benzanthracene tested for carcinogenic activity in mice.

(4657) Silberberg & Silberberg; Jewish Hospital, St. Louis, MO: inhibition of wound epithelization in mice treated with benzpyrene or methylcholanthrene.

(4659) Stowell & Maas; Washington University, St. Louis, MO: large doses of methylcholanthrene painted on skin caused systemic effects in mice.

(4660) Strong; Yale University School of Medicine, New Haven, CT: hybrid mice resulted in resistance to induced tumor by methylcholanthrene.

(4661) Strong; Yale University School of Medicine, New Haven, CT: genetic principles that control cancer.

(4726) Cowdry; Washington University, St. Louis, MO: epidermal carcinogenesis and hypersensitivity.

(4891) Thomas & Stetson; Johns Hopkins University, Baltimore, MD: Schwartzman phenomenon from topical application of bromobenzene.

Chester Beatty Research Institute, Cancer Hospital (Free), London, GBR. Kennaway & Kennaway and their collaborators pioneered in the identification of carcinogens in coal tar and related fossil fuel products. They were also credited for the combined use of chemical analysis, isolation, synthesis, and biologic testing in the identification of four reference compounds, namely, dibenzanthracene, benzanthracene, benzopyrene, and methylcholanthrene. Their publications relating to

experimental skin cancer in mice are listed below in chronological sequence starting in the early 1930's.

(3233) Cook, Hieger, Kennaway & Maynoerd: testing for cancer producing action of polycyclic aromatic hydrocarbons.

(3333) Cook, Hewett & Hieger: isolation of benzopyrene from coal tar.

(3544) Barry, Cook, Haslewood, Hewett, Hieger & Kennaway: testing of tetracyclic and pentacyclic aromatic hydrocarbons.

(3740) Bachman, Cook, Dansi, de Worms, Haslewood, Hewett & Robinson: testing in mice and rats of about 140 compounds.

(3741) Cook, Haslewood, Hewett, Hieger, Kennaway & Mayneord: test of cholanthrene derivatives.

(4022) Badger, Cook, Hewett, Kennaway, Kennaway, Martin & Robinson: testing of 70 additional compounds.

(4515) Burrows, Roe & Schober: electrical action potential differences in skin of mice during carcinogenesis.

(4942) Hieger: review of chemical carcinogenesis.

During the late 1940's, scientists at the Chester Beatty Research Institute turned their interest to carcinogenic compounds not present in coal tar, as well as anti-cancer agents (see Topic E).

<u>Other cancer research laboratories in Great Britain</u>. The most significant contributions from British academic institutions are listed below. Details on "cocarcinogenic action" on mouse skin were reported for the first time.

(4123) Berenblum; Oxford University Centre of British Empire Cancer Campaign:

"The effect of croton resin on carcinogenesis was studied under varying conditions, in order to determine the nature of cocarcinogenic action (the argumentation of carcinogenesis which occurs when croton resin is applied to the skin concurrently with a dilute solution of 3,4-benzpyrene) and its relation to the normal process of carcinogenesis. No cocarcinogenic effect was observed when the croton resin was applied to the skin and the benzpyrene was injected at a distance (intra-peritoneally); nor was it possible to augment the carcinogenic effect of benzpyrene on subcutaneous tissues, by injection of croton resin together with the benzpyrene. While augmentation of carcinogenesis was very pronounced when croton resin was applied to the skin concurrently with a dilute solution of a potent carcinogen (3,4-benzpyrene), none was observed with concentrated solutions of different carcinogens, irrespective of whether their potency were high (3,4-benzpyrene), moderate (1,2,5,6-dibenzanthracene), or very low (1,2-benzanthracene). Preliminary treatment with croton resin for a period of 26 weeks failed to influence significantly the response of the mouse's skin to subsequent applications of benzpyrene. On the other hand, croton resin applied to the skin subsequent to a limited period of benzpyrene treatment led to a striking increase in the development of tumors. Croton resin applied to papillomas already established appeared to facilitate their conversion to malignancy. **From consideration of these results, the suggestion is put forward that the three phases of carcinogenesis - (a) the development of the preneoplastic phase (latent period), or precarcinogenic action, (b) the conversion of this into the wart stage, or epicarcinogenic action, and (c) the malignant transformation of these warts, or metacarcinogenic action - are probably not simply stages of one single carcinogenic process, but independent processes.** The carcinogenic hydrocarbons possess all three actions; croton resin possesses only the second and third, and cannot, therefore, produce tumors by itself. No precise knowledge is yet available as to the nature of cocarcinogenic action, but two possible modes of actions are discussed.

The most significant experiment was that in which the croton resin was applied to the skin in conjunction with 1,2,5,6-dibenzanthracene and 1,2-benzanthracene respectively, and, apart from the conclusions which have

already been reached from this experiment, the results also help to throw a little light on the mechanism of cocarcinogenesis. The simplest conception of cocarcinogenic action would be that it was merely a variant of epicarcinogenic action, on the supposition that the dilute benzpyrene produced the preneoplastic state, while the epicarcinogenic effect was carried out jointly by the dilute benzpyrene and the croton resin. If this were the case, one would have to assume, first, that the precarcinogenic action of benzpyrene is less influenced by dilution than its epicarcinogenic action and, second, that the low carcinogenic potency of dibenzanthracene and the still lower potency of benzanthracene are due primarily to deficiencies in precarcinogenic action. Until these assumptions are confirmed experimentally it is not possible to say whether this simple explanation of ccocarcinogenic action is correct or not. An entirely different explanation of the mode of action of cocarcinogenesis would be to suppose that croton resin merely facilitated the entry of the carcinogen into the cell so that a small number of molecules of the hydrocarbon, applied to the surface, would still have a reasonable chance of acting on the cell. This would account for the failure of croton resin to augment carcinogenesis in the case of concentrated solutions of carcinogens, irrespective of whether their potencies are high, medium, or low. This interpretation implies, however, that cocarcinogenic action is an entirely different process from pre-, epi-, and meta-carcinogenic action. No decision can be made at the present stage as to the likelihood of this explanation being the right one." pages 813-814, (4123)

(4416) Berenblum; University of Oxford, GBR:

"Many books and reviews and innumerable other publications have appeared from time to time with the set purpose of finding a solution to the problem of the part played by irritation in the development of a tumor. Some of these publications are noteworthy for the patience and the care displayed by the authors in searching through the literature for all references that may have any bearing on the problem. Unfortunately, such reviews commonly suffer from insufficient critical judgment, whether dealing with mere expressions of opinion, with casual observations or with detailed results obtained from statistical analyses. Some publications place critical judgment in the forefront of the work, but among these the 'judgment' is sometimes carried too far, tending toward irrational skepticism.

Publications confined to statistical analyses are more useful, provided the nature of the irritant is carefully specified in every case and other postulates are rigidly applied. But most publications are concerned with a few cases personally observed by the authors and with such citations from the literature as happen to support the particular thesis they wish to stress. Perhaps the fault of the majority of publications on the subject lies in the fact that the question posed - Is irritation the cause of tumor formation? - is too simple. The result of such an inquiry tends to resolve itself into a statement as to how many authorities are for this view and how many are against. Unfortunately, decision by majority is not the best means of establishing scientific truth.

The evidence indicates that preneoplastic hyperplasia is a highly specific type of hyperplasia since only carcinogenic irritant can produce with certainty, but that once the preneoplastic state has been induced (by a true carcinogen) a benign tumor can be made to appear at that site and a tumor already present can have its progress to carcinoma hastened, by the action of a variety of noncarcinogenic irritants. If this is confirmed, the following practical lessons will have been learned: (a) that there is little danger of an ordinary irritant producing a tumor of its own accord; (b) that this applies also to the initiation of a preneoplastic lesion; (c) that, given a preneoplastic lesion, the subsequent development of a benign tumor at the site may be facilitated, and its progress to cancer hastened, by the action of a variety of nonspecific irritants. It is a comforting thought, however, that with most nonspecific irritants this facilitation is far less effective than it is with a true carcinogen."
pages 243-244, (4416)

(4417) Berenblum & Schoental; University of Oxford, GBR:

"A sample of blue shale oil was found to be strongly carcinogenic to the mouse's skin, whereas a concentrated extract of shale (the natural product from which shale oil is obtained by retorting) failed to produce any tumours after 40 weeks of painting. These results confirm the view, previously expressed by the authors, on the evidence of fluorescence analysis of chromatographic fractions of shale oil and extract of shale, that the carcinogenic constituents of shale oil do not exist in the original shale, but owe their presence to pyrolytic effects during the retorting."
page 96, (4417)

(4428) Crabtree; Imperial Cancer Research Fund, Mill Hill, London, GBR: carcinogenic action of 3,4-benzpyrene on mouse skin was inhibited and sometimes prevented by local application of bromobenzene.

(4519) Crabtree; Imperial Cancer Research Fund, Mill Hill, London, GBR: carcinogenic action of 3,4-benzpyrene and 1,2,5,6-dibenzanthracene on mouse skin was greatly retarded by maleic and citraconic anhydrides.

(4544) Lea; Strangeways Laboratory, Cambridge, GBR: mean of logarithms of induction times proposed as means of summarizing results of carcinogen assay.

(4561) Pullinger; Imperial Cancer Research Fund; multiple simple excisions from mouse skin treated with benzpyrene stimulated tumor formation.

(4564) Riley & Pettigrew; Wilkie Surgical Research Laboratory, University of Edinburgh, GBR: mechanical irritation caused accelerated carcinogenesis in skin of mice painted with 1:2:5:6-dibenzanthracene.

(4611) Armstrong & Bonser; University of Leeds, GBR: retesting of mice sensitive to benzpyrene.

(4617) Dickens & Weil-Malherbe; North England Council of the British Empire Cancer Campaign, Newcastle-upon-Tyne, GBR: anticarcinogenic action in certain samples of mouse fat is due neither to content of unsaturated fatty acids nor of saturated

one. Rate of elimination of benzpyrene bore no relationship to carcinogenic nature of solvent.

(4639) Irwin & Goodman; Medical Research Council, London, GBR: statistical treatment of carcinogenic properties of tars and mineral oils conducted by Twort & Twort on mice.

(4665) Weil-Malherbe & Dickens; Newcastle-upon-Tyne, GBR: influence of cholesterol and phospholipids on tumorigenic effects of benzpyrene injected subcutaneously in mice.

(4711) Anderson; London, GBR: physico-chemical aspects of chemical carcinogenesis.

(4715) Berenblum; Oxford University Research Centre of the British Empire Cancer Campaign: analysis of cocarcinogenesis from results of Berenblum, of Rouse and his associates, and of Mottram. Note that concept of cocarcinogenesis was derived from skin painting studies.

(4716) Berenblum & Schoental; University of Oxford, GBR. Further attempts to understand mechanism of carcinogenesis in experimental skin painting in mice:

> "1. In order to study the stages of carcinogenesis by quantitative means, use was made of the technique, based on Mottram's work, whereby tumours of the mouse's skin may be induced by a single application of a carcinogen, followed by repeated applications of croton oil. 2. When the croton oil treatment was kept constant but different carcinogens were used for the initial painting, the tumour incidence varied from group to group but the average latent period remained the same. 3. When the initial painting with the carcinogen was kept constant but the croton oil treatment was delayed, the tumour incidence remained the same but the latent period varied, corresponding approximately to the lengths of the intervals free from treatment. 4. It was

concluded that the initial action in carcinogenesis constitutes a sudden and irreversible process, whereby a few normal cells are changed into permanently altered 'latent tumour cells,' which lie dormant among the non-neoplastic cells. **The mechanism by which these latent tumour cells are made to develop into tumours is altogether different from that of the initial transformation."** page 164, (4716)

(4717) Berenblum & Shubik; University of Oxford, GBR

"A carcinogenic tar was fractionated by (1) extraction with solvents, (2) chromatography on alumina columns, (3) high vacuum distillation, and (4) crystalization, formation of picrates, etc. The fractions were tested for carcinogenic activity, by skin painting in mice and rabbits, and for benzpyrene content, by fluorescence spectrography." page 390, (4717)

(4722) Calcutt & Powell; Radium Institute, Northwood, Middlesex, GBR: clipping of fur is best preparation of skin; mice very rapidly lick off any reagent applied to skin.

(4730) Dickens; Courtauld Institute of Biochemistry, Middlesex Hospital Medical School, London, GBR: influence of nature of solvent on carcinogenic response of 3,4-benzpyrene in mice.

(4789) Weil-Malherbe; King's College Medical School, Newcastle-upon-Tyne, GBR: effect of lipoid solvents on rate of elimination and the carcinogenic potency of 3,4-benzpyrene after subcutaneous injection in mice.

(4790) Weil-Malherbe; Newcastle-upon-Tyne, GBR: elimination and carcinogenic potency after subcutaneous injection in nonlipoid solution.

(4812) Badger; University of Glasgow, GBR: chemical structure and carcinogenic activity; review of 20 years research on polycyclic aromatic hydrocarbons.

Co-carcinogenicity of wood soot. Sulman & Sulman, from the Hebrew University in Jerusalem, collected the soot from the chimney of a smoked sausage factory. The results from experiments on rats were as follows:

> "Thirty-six female rats implanted subcutaneously with fragments of soot from the chimney of a sausage factory developed sarcoma in 16.6 per cent of the cases. No tumor developed in 36 male rats implanted intrascrotally with bits of the same soot. Ten female mice treated for 2 years with an ether and alcohol extract of wood soot showed tumor formation in 3 cases (2 sarcomas and 1 carcinoma). Twenty rats fed for 2 years on a diet containing an unlimited amount of smoke sausage failed to develop tumors. The conflicting finding, carcinogenic effect in parenteral treatment versus absence of carcinogenic effect after oral administration, indicates the need for further study of the carcinogenic activity of smoked food, in view of the practical importance of the problem for human nutrition. The consumption of smoked sausage over a period of more than 2 years did not cause tumors in rats. However, the wood smoke used for its preparation was shown to contain substances that were carcinogenic for rats when introduced subcutaneously, and for mice when rubbed into the skin. The sarcomas obtained in 16.6 per cent of the rats following the implantation of soot particles may not appear significant, in view of the finding by Turner that sterile bakelite disks, when similarly implanted in rats, elicited sarcomas in 31 per cent of the animals. **Our finding became significant, however, by reason of the carcinogenicity of the soot extracts for mice (33.3 per cent) when rubbed into the skin.** A further study of the possible carcinogenic role of wood soot extracts therefore seems desirable." page 367, (4663)

Like all other skin painting experiments, the above on soot extracts with positive results were not applied to speculate on

cause of lung cancer associated with inhalation of industrial pollutants.

Animal Experiments of Industrial Pollutants that are also Cigarette Smoke Constituents

The last section on occupational/environmental factors is concerned with studies relating to industrial chemicals that coincidentally are present in cigarette smoke and 'tobacco tar.' Although their presence in tobacco smoke and industrial emissions has been recognized during the 1940's, differences in concentration have been overlooked. The political situation in Europe and the United States during the 1940's had influenced the credibility of German scientists, including the Nazi doctors, who conducted toxicologic research in human prisoners. After World War II, it became apparent that intravenous phenol was used for selective euthanasia. During the early years of Nazism, some German scientists published that phenol was a naturally occurring substance in the human body. Also during the late 1930's, German scientists wrote the first complete monograph on toxicity of industrial chemicals that was translated into English by authority of the Alien Property Custodian (4304). It is not known how much of these chemicals were tested in concentration camps and only phenol has been identified. The materials relating to Nazism in medicine are being submitted in the form of two monographs (8601) (8602), and an article on occupational

cancer among Jewish and non-Jewish population of the Netherlands (4978).

Benzpyrene in tobacco tar. Hieger, from Research Institute of the Royal Cancer Hospital, London, was credited as the first scientist who characterized the fluorescence spectrum of 3:4-benzpyrene (3739). He used visual examination of photographs of fluorescence spectra, and patiently separated, isolated and identified 3:4-benzpyrene from coal tar pitch. The synthetic solution of benzpyrene was used to identify and separate it from contaminants in coal pitch. Tobacco tar tested by Hirst did not contain the fluorescence bands characteristic of benzpyrene (3230). Roffo & Roffo Jr. reported isolating benzpyrene in 1939 and 1940 (3942) (4017). Roffo used destructive distillation whereas Hirst collected tobacco tar at a lower temperature. Also in 1940, Roffo proposed legislation on prevention of cancer associated with industrialization (4019). This article needs to be added to Spanish publications needing English translation.

Benzpyrene was not tested by inhalation in experimental animals because a chamber designed to administer the substance in an appropriate solvent was not yet available. Carlson and Adams, from the University of Chicago, surgically produced persistent bronchial fistulating rats and rabbits specifically for the purpose of direct application of suspected carcinogens to the bronchial mucosa. I have selected their report as a highlight publication (4326). Three months of applications, every other

day, did not induce any definite "gross evidence of cancer." I have not found a followup article on microscopic examination of tissues and detailed results of studies that were in progress.

Oxides in tobacco smoke and fuel combustion. Carbon monoxide was the most widely investigated constituent of tobacco smoke and fuel combustion (2701) (3339) (4206) (4261). Carbon monoxide had not been suspected as a carcinogen. However, animals exposed to low levels of carbon monoxide were less sensitive to tar skin cancer in mice (3636). The influence of carbon monoxide was attributed to reduction of oxygen carrying capacity of blood nurturing the tumor. Nitrogen oxides were generated both in burning of tobacco and fossil fuels. The potential dangers of nitrous fumes in industry were reviewed by von Oettingen (4174).

Aliphatic and aromatic compounds. During the 1930's and 1940's, monographs on toxicology were written by McNally (3783) (3902), Lehmann & Flory in German and translated to English by King & Smyth (4304), and Henderson & Haggard (4302). Phenol vapor was tested in animals because of its antiseptic use (4430). The inhalation effects of hydrocyanic acid fumes consisted of pneumonitis in animals (3134). Ingestion and metabolism of polycyclic hydrocarbons were the subject of animal experiments (4327) (4522). Results of animal toxicity studies were applied to patients establishing safety margin of drugs (3972) and worker exposure (4855). The concentrations of aliphatic and aromatic

compounds in cigarette smoke are so low that it would take hundreds of thousands of cigarettes to approach work standards (see Part Four).

Heavy metals in tobacco smoke. During the 1940's, trace levels of arsenic were detected in tobacco and tobacco smoke (4370) (4575). Arsenical insecticides were the origin of the contaminant (3461) (3568). Arsenic in tobacco smoke was suspected as the cause of lung cancer in cigarette smokers (4619) (4950). This suspicion was based on the observation of skin cancer in workers exposed to arsenic (3332) (3550) (4158) (4239) (4570) (4728) (4878). That workers exposed to arsenic developed lung cancer was based on epidemiologic studies (4770) (4839) (4873). Animal studies could not replicate tumors seen in human workers (_____). Cadmium was a known industrial hazard (4714) (4777) but its human carcinogenicity was not accepted until after 1950.

Awareness of literature prior to 1950. Most of the articles under Topic D and Topic E are simply listed without commenting on the validity of their contents. The articles are listed for completeness because most of them were used as citations in references for Part Three, literature review from 1950 to 1966.

E. HOSTAL SUSCEPTIBILITY FACTORS

The monograph entitled *Bronchogenic Carcinoma and Adenoma* by Fried was published in 1948 (a revision of an earlier one published in 1930) and is a **highlight publication.** In the latter edition, Fried concluded that evidence thus far adduced was contrary to the idea that bronchiogenic cancer was caused by tobacco, page 68, **(4801).** On the other hand, Fried accepted the multiplicity of causes attributed to the lung "as an organ that receive dust, bacteria, fumes, gases directly from the air" and "as an organ of convergence of the body ... reached by soluble and particulate matter via the systemic circulation." Fried enumerated factors influencing susceptibility of host such as genetic, diet and nutrition and cellular responsiveness to dust inhalation, infectious disease and trauma. There was an artificial dividing line between dust inhalation covered under Topic E, from occupational/environmental factors under Topic D. For the purpose of this review, chemical vapors, gases, and organic substances, including fossil fuel and combustion emissions are discussed under occupational/environmental factors (Topic D). Occupational hazards consisting of dust particles are discussed under Topic E because of their unique nature in provoking fibrosis and occasionally, lung cancer in susceptible individuals. Inhalations of asbestos and silica are discussed under Topic E because the response is attributed directly to

particulate rather than to a chemical substance or polycyclic aromatic hydrocarbon.

Heredity

Many research contributions on factors determining susceptibility of cancer in mice were derived from inbred strains that were in existence during the 1940's. The following laboratories had strains that either had a high or low incidence of spontaneous tumors and were suitable for investigation of carcinogenic chemicals: National Cancer Institute (4234) (4235), Rockefeller Institute for Medical Research (4058), Jackson Memorial Laboratory at Bar Harbor, ME (4057), National Institute for Medical Research at London (4222), Royal Cancer Hospital at London (4448), University of Leeds (4613), Cornell University Medical College (4121), University of Chicago Medical College (4120), and Yale University Medical School (4474). Strong, from the last mentioned laboratory, attempted to duplicate or imitate in experimental animals the variable genetic background of man. By hybridization of mice and selection toward resistance to methylcholanthrene-induced local tumors, Strong was able to produce selected strains of mice for cancer research (4474). Little, from Jackson Memorial Laboratory, described the incidence of mammary tumor in inbred mice and concluded that the occurrence was dependent not only on genetic constitution but also on physiological variation in the host (4057). Reimann

favored the genetic theory as the cause of cancer and wrote several reviews (4562) (4563) (4959).

Genetic studies in humans have revealed familial aggregation of breast and uterine cancer in pedigree families (4775) (4921). A familial factor had been reported for gastro-intestinal cancer and xeroderma pigmentosa (4448). Twin research revealed genetic susceptibility to tuberculosis (3984). However, it would take two decades later for twin research to support genetic susceptibility to lung cancer. During the 1940's there were several reviews on congenital bronchial adenoma implying that some forms of lung cancer may originate from congenital adenoma (4139) (4232) (4337) (4362) (4514) (4845).

The most significant review on genetic aspects of the cancer problem was prepared by Fritz Blank of New York, under the auspices of the Council of the Bureau of Human Heredity (London) and the Genetics Laboratory, Ohio State University (Columbus, OH). This is a **highlight publication (4418)**. There was a discussion of lung cancer in experimental animals induced by coal tar, but no discussion of human lung cancer. The seven summary statements were as follows:

> "A summary of the present position meanwhile shows that enough evidence has been accumulated to warrant at least the following statements: A. Cancer is not a unit disease, at least so far as its genetic behavior is concerned. Tumors of different sites and types differ in their genetic behavior. B. Therefore it is unlikely that a heritable condition of 'cancer' exists as such. Or, as Haldane has put it: 'The genetics of spontaneous cancer is clearly very complicated, and it is quite ludicrous to ascribe it to the activity of one gene,

> dominant or recessive.' C. There does exist a general inherited disposition, whether of susceptibility or refractoriness, to formation of tumor. By the term 'susceptibility' should be understood the ability of the body to react to specific stimuli with formation of tumor. By the term 'refractoriness' is meant a condition which seems to make the formation of tumors impossible even in the presence of appropriate stimuli. D. In certain persons, factors exist, most probably inherited independently of a general disposition, which govern the localization of the disease. This localization in turn seems to depend on a favorable 'internal environment' in certain tissues or organs. E. If general susceptibility and inherited favorable internal environment are combined in an individual, these factors may be strong enough in themselves to lead to formation of cancer in certain tissues. F. If general susceptibility is great in an individual, even relatively slight irritation by agents of many kinds may lead to formation of cancer. G. But apart from these heritable conditions, there exist purely external cancerogenic agents of various kinds, which are obviously strong enough to lead to formation of cancer in certain tissues, even in persons in whom an inherited predisposition is not distinct or perhaps is too weak to be detected by methods used at present in testing for hereditary traits. Or the predisposition to cancer may not have been inherited but rather acquired under conditions the nature of which is not yet known." page 314, (4418)

Blank's survey of "constitution" as related to cancer will be one of several background papers for the proposed "constitutional hypothesis" prepared after 1950 to explain high incidence of lung cancer in cigarette smokers (See Chapter V).

Diet and Nutrition

Following Hoffman's monograph on *Cancer and Diet* (3701), there was no comprehensive review on the subject during the 1940's. A few authors wrote reviews on carcinogens that included a discussion on influence of diet on susceptibility of

animals to administered carcinogens: Morris, from the National Cancer Institute, reviewed the influence of diet on spontaneous lung tumor formation in mice (4553); Tannenbaum, from Michael Reese Hospital, Chicago, published a series of articles on the effects of feeding, bodyweight on spontaneous and induced skin and hepatic tumors (4093) (4094) (4265) (4475) (4476) (4574) (4970) (4971). Other investigators confirmed the influence of diet and nutrition on tumors in mice induced by benzpyrene (4025) (4918), methylcholanthrene (4662) (4949), and azo compounds (4449) (4452) (4540) (4541) (4769) (4860) (4861). An extrinsic factor in human liver cancer was suspected (4447) but was not identified until two decades later. The following food ingredients have been reported to cause experimental tumors: choline deficiency (4616) (4734) (4924), desoxycholic acid (4415), pyrrol compounds (4435), fat solvents (4525) (4526) (4957), heated cholesterol (4774) (4844) (4930), and tomato juice (3133) (3243). The relevance to human cancer of some of these compounds was not known during the 1940's, other than the structural relationship of cholic acid and pyrrol compounds to methylcholanthrene.

Repeated Bronchopulmonary Irritation

Macklin questioned the importance of chronic respiratory tract irritation relative to constitutional factor and heredity in the etiology of lung cancer (4857). Their

article is selected as a highlight publication:

"As with all other cancers, the problem of the origin of primary cancer of the lung naturally divides itself into two aspects concerned with (1) supposed productive factors acting from outside the body and (2) constitutional factors inherent in the body and varying with the patient and particularly with the 'strain' or line of descent. These agencies are characterized as environmental and hereditary, respectively. The environmental factors may be subdivided into two categories: (a) those that would be encountered in the course of ordinary living, which are the various chronic irritants commonly used to explain human cancer, and (2) those which have been discovered by inducing cancers in animals through the experimental use of specific chemical agents, called carcinogens. As man is not used in the experimental production of cancer, all malignant growths arising in him must come under the heading of (1) tumors induced by the chronic irritations of ordinary life or (2) tumors arising on account of constitution. These may be considered as primary poles, or extremes, useful in our mental processes in the study of the causes of cancer. Actually, the constitutional factor enters into every production of tumor, and the only point which needs to be determined with reference to it is the extent to which it is participating in any given case. So, if the environmental factor is admitted, all tumors are of dual origin. In conclusion, then, we may say that none of the specific diseases or conditions causing chronic inflammation of the lungs can be said to have been proved to be causes of cancer of the lung. They have not been shown to be more common in patients with pulmonary cancer than in a group of the general population of similar age and sex, and until a significant difference can be found between their incidence in those with pulmonary cancer as compared with those without pulmonary cancer their causal relation to this type of cancer will remain purely speculative. This, of course, refers to chronic inflammatory diseases which have antedated the cancer by a sufficient number of years so that they can be excluded from being interpreted as the result, not the cause, of the cancer.

Chronic irritation, especially in the form of chronic inflammatory disease, as a cause of pulmonary cancer has been assumed; the idea has been copied from text to text, repeated from author to author, with little critical analysis of its possible role. Somatic mutations and hereditary factors must be considered and their probable role in causing cancer of the lung

> recognized. True carcinogenic agents for the production of cancer of the lung will no doubt be found as modern industry expands its use of chemicals. But, as some types of cancer will develop in one seventh of men over 40 and since about one fifth of all cancer in males are in the lungs, one thirty-fifth, or about 3 per cent, of all men over 40 will die of this type of cancer. There may be an increase in the incidence of cancer of the lung in any industry beyond the maximal rate for cancer of the lung in the general population, **but one can never state that any patient would not have had cancer of the lung had he not been in that occupation.** Thus even with the presence of carcinogenic agents admitted, their role in causing cancer of the lung cannot be proved in any individual case, nor can they be said to be 100 per cent effective, since a certain percentage of persons exposed to the carcinogenic agents would have had pulmonary carcinoma even without this exposure. The effectiveness of any carcinogenic agent in producing carcinoma of the lung can be judged only by the increment of increase of carcinoma of the lung in large groups, not by its total incidence. It is therefore impossible to assign to any extrinsic factor an absolute role in carcinogenesis in any individual case." pages 926, 954-955, **(4857)**

The above comments were applicable through the 1960's. Even in 1989, it is still "impossible to assign to any extrinsic factor an absolute role in carcinogenesis." It is "impossible" to assign an absolute causative role of cigarette smoking in a lung cancer patient.

Repeated Chemical Irritation. The reaction to repeated inhalation of chemicals, vapors, gases, and substances, consist of cellular death, regeneration metaplasia repair (12112). It has been proposed that repeated exposure of skin to chemical irritants would lead to cancer and this has been supported by repeated skin painting with coal tar or its constituents in mice. However, repeated inhalation of cigarette smoke or chemical vapor and gases have not caused experimental lung cancer (See Topics C

and D above). The following chemicals administered orally or parenterally caused tumors of several organs including the lungs: urethane (4338) (4354) (4757) (4762) (4864) (4925); dinitrotoluene (4426); nitrogen mustards (4817) (4818) (4941); 2-aminofluorene (4843); sulfonamides (4836); and DDT ((4737).

Hueper reported that the intravenous injections of methyl cellulose or polyvinyl alcohol caused pulmonary thesaurosis and atherosclerosis but no neoplasm in rabbits and dogs (3950) (4208) (4238) (4444) (4534) (4537). Prior to 1950, chemical substances administered intravenously could produce lung cancer but it was not known if the cellular mechanism was similar to that elicited by repeated irritation from a chemical inhalant.

Chronic dust diseases of the lung. The association of lung cancer and occupational exposure to dust continued to be reported during the 1940's. The following dust particles were suspected pulmonary carcinogens: asbestos fiber (4090) (42134) (4159) (4228) (4236) (4258) (4268) (4339) (4366) (4439) (4625) (4641) (4650) (4658) (4729) (4824) (4850) (4912) (4927) (4967) (4975); silica (4349) (4358) (4746) (4776) (4837) (4838) (4898) (4967); boiler scaling particles (4433) (4441) (4478) (4517) (4745) (4928); beryllium (4631) (4895); chromate dust (4851) (4852); coal dust (4749) (4958); brick clay for brickworks (4945); diatomaceous earth (4892) (4973); abrasive materials (4779) (4884) (4911); and lead (4036) (4321). These publications were not included in Hueper's monographs that appeared early in the

1940's. The investigation of lung cancer in workers exposed to dust was continued after the 1950's and some of them were tagged as "known carcinogens" by the National Toxicology Program.

Pulmonary tuberculosis and fibrogenic agents. During the 1940's, the differential diagnosis between tuberculosis and lung cancer continued to challenge internist but not as frequently as in earlier decades (4076) (4558) (4913). There was still some suspicion that pulmonary tuberculosis caused tissue reaction that rendered the lung susceptible to chemical or non-chemical carcinogens (4061) (4246) (4961). The basic cellular response consisted of fibrosis which supposedly caused the appearance of cancer in the wall of tuberculous, bronchiectatic and emphysematous cavities (4046) (4360) (4578) (4780). The combination of silicosis and tuberculosis had contributed to the confusion in determining the basic causation of lung cancer (4654) (4791) (4917) (4972).

Physical agents. Radiation continued to be a suspected cause of lung cancer during the 1940's. The specific forms were as follows: radium contained in ores mined at Schneeberg and Joachimsthal (4455); gamma radiation (4645) (4948); ultraviolet radiation (4419) (4420) (4565); and cosmic radiation (4535) (4536) (4934). Additional physical agents have been examined for carcinogenic activity: trauma (4365) (4453) (4479) (4569) (4620) (4630) (4655); and ultrasonic vibration (4830). Henshaw, from the National Cancer Institute wrote a review of physical

carcinogens including mechanical irritation or injury caused by stems of clay pipes in lip epithelioma (4532). The implantation of bakelite discs leading to sarcoma in rats was another example of physical agent causing cancer (4172).

Pulmonary adenomatosis and viruses. Two forms of lung cancer had been suspected as of viral etiology: adenomatosis (4580) (4969), and alveolar cell carcinoma (4066) (4151) (4248) (4368) (4538) (4947). It was believed by some pathologists that both forms originated from the same cell in the lung. In later decades it had not been possible to isolate and transmit any virus from human lung tissue samples although the possibility of viral etiology of lung cancer has not been completely excluded. Techniques that successfully demonstrated papilloma virus in rabbits (4026) (4080) (4167) (4842) and spontaneous tumors in animals (4559) (4581) (4628) (4743) (4834), represented transmission within the same animal species. Isolation of virus from human cancer tissue for transmission to animal species has not been possible. The 1989 nobel laureates in medicine were credited with the discovery of viral induced genetic mutation resulting in cancer.

Environmental and Hostal Interactions

Most information on the subject of interactions between environmental etiologic factors and the susceptible host were derived from experimental animals. During the 1940's and earlier

decades, the need to verify occurrence of interaction in lung cancer patients was implied in review articles on experimental carcinogenesis by the following: Gye (4531); Ivy (4756); Haddow (4629) (4742) (4744); Sannie & Truhaut (3471); and Schabad (2846) (3248) (4571) (4582).

Respiratory tract interactions. The following inhalants have been tested in experimental animals: coal smoke in rabbits (3797); silica and iron oxide in mice (4027); silica and methylcholanthrene (4221); steel grindings in mice (4221); and benzpyrene and several samples of tarred road dust, coal dust, and coal soot in mice (4325). Campbell's conclusions follows:

> "There is a similarity between human lung cancer and mouse lung cancers as regards: (1) agents which increase the incidence of these tumours; (2) the time or age factors; (3) some aspects of the factor of susceptibility; (4) morphology of the tumours. Although the main effect of certain dusts in development of lung cancer appears to be of a prolonged chemical nature, it is not possible at the moment to exclude entirely some effect of prolonged mechanical irritation by the harder or larger collections of dust. A method for comparison of the degree of dust deposit in the various experiments is given for the first time. The increase in incidence of lung tumours in mice by certain dust - tarred road dust with and without the tar, Czechoslovak pitchblende dust, iron oxide, silica, a 'nickel' dust mixture - is statistically significant, although in most cases the average deposits of dust in the lungs are of moderate degree only or less. Care should be taken to reduce exposure to these dusts. Dusts produce a hypertrophy of lymph tissue in the lungs and in the tracheo-bronchial lymph nodes. Some further illustrations of mouse lung cancers and their metastases are given. There is no fundamental reason why the results obtained in mouse experiments with dusts should not be applied to man." page 183, (4325)

In a later issue of the British Medical Journal, Campbell defended his conclusions:

> "After referring to the high incidence of lung cancer in the Schneeberg and St. Joachimsthal miners, attention is drawn in the leading article to the diffrences between the mouse and human lung tumours. It is stated: 'The first and most obvious [difference] is that lung tumours are exceptionally common in some strains of mice; their incidence in control animals in some of these experiments was 20.' I cannot see how this differs from the condition in the above-mentioned miners. Surely, it is a resemblance, not a difference, between the mice and human beings. Further, it is stated that in mice the lung tumours is usually an adenoma in which malignant change is the exception. This was certainly not the case in the experiments with the dusts, where the malignant tumours were more numerous than the simple adenomas. I have not stated that nodular silicosis gives rise to cancer of the lung. My mice did not develop nodular silicosis of the lung during the dusting with silica, although the incidence of lung tumours was definitely increased and there were silicotic nodules in the tracheo-bronchial lymph nodes of about half the mice. In a previous paper I have suggested that when silicosis of the lung - i.e., the nodular condition - develops it may inhibit cancer development. Further, silicosis itself may be consider-ed a type of multiple tumour, although not malignant, of course. In my experiments with iron oxide dust the resulting tumours were more numerous and more malignant than those produced by silica dust. I consider iron oxide at least as active as silica in the case of mice and man. At no time did we find the dusting experiments tedious, since we were the first (1932-4) to obtain positive results. This is due to paying proper atten-tion to the time and other factors. Other researches obtained negative results because their experiments were of too short a duration or they used non-susceptible animals as subjects. The main object of our experiments was to obtain clues to prevention or cure of lung cancer - a difficult problem and not easy to approach." pages 269-270, (4324)

During the 1940's, there were studies on nasal filtration of airborne droplets in rabbits (4720), dust deposition in human tracheobronchial passages (4926), and clearances of carcinogenic

dust particles in workers (3874) (4041) (4322) (4719) (4721) (4738) (4963). The techniques for dust deposition and clearance were not tested for cigarette smoke. Prior to 1950, the only reported airway effect of cigarette smoke was on tracheal cilia of calves (3784).

Airway irritation. The widely accepted theory for pulmonary carcinogenesis prior to 1950 was "irritation" that was widely popularized by Simon's monograph (3702). Several clinicians and pathologists accepted the irritation theory (4129) (4161) (4169) (4253) (4259) (4355) (4768) (4866). Several stages relating to formation of skin cancer were demonstrable in experimental animals (4520) (4543) (4636) (4642) (4653). For pulmonary carcinogenesis, it was not possible to identify in sequence, from initial irritation, pre-neoplastic changes to final cancer in the same group of animals exposed to carcinogens. There were studies on role of respiratory tract on metastasis (4626), and the susceptibility of human lung to second type of cancer after removal of a primary lesion (4479). However, there were no reported observations relating to pre-neoplastic lesions evolving into lung cancer in the same patient.

Biochemistry of cancer. After World War II, the increase in cancer research extended to include biochemistry. There were review articles on the differences between normal and cancerous patients, and the influence of chemically induced cancer in experimental animals (4301) (4423) (4470) (4530) (4579) (4875)

(4880) (4889). There were also reviews on the metabolism of chemical carcinogens, particularly of polynuclear aromatic hydrocarbons (4618) ((4761) (4881) (4976).

Intrinsic carcinogens. During the 1940's, there were reports that extracts from cancerous tissue caused tumors after injection in experimental animals (4459) (4750) (4785) (4786) (4787). The chemical identity of intrinsic carcinogenic factor was not known although hormones were excluded. The growth of some non-pulmonary tumors was influenced by hormones from pituitary (4465) (4664), adrenal cortex (4766) (4940), testis (4627), and ovaries (4438) (4741) (4825). A milk borne tumorigenic agent was detected but not chemically identified in mammary adenoma in mice (4512) (4778). Also in mice, bronchogenic carcinoma was induced from subcutaneous grafts of adult lung tissue impregnated with methylcholanthrene. The tumor incidence was increased if lung grafts were impregnated with stilbestrol in addition to carcinogen. Stilbestrol or other estrogens injected alone did not cause lung carcinoma (4220) (4752). There were early reports of sensitization to tumor cells that prevented successful transplantation directly to lung tissue (4335) (4462) (4463) (4919).

Inadequate scope of cancer research. Although there was a considerable increase in human and financial resources for cancer research after World War II, there were criticisms on the following: First, lack of improvement in treatment of cancer

(4840); Second, need for emphasizing nutritional, cellular and molecular basis for carcinogenesis (4542) (4553) (4577) (4643) (4739) (4764); Third, need to identify responsibility for delay in cancer diagnosis and its correction (4468) (4573) (4763) (4885); and Fourth, selecting human carcinogens among growing list of animal carcinogens (4224) (4429) (4545) (4846) (4923). Most attempts at confirming the carcinogenicity of some chemicals, including constituents of tobacco smoke, and tobacco smoke per se and tobacco tar, gave negative results. The comments of Pfeiffer & Allen from Yale University of School of Medicine, on their attempts to produce cancer in rhesus monkeys with carcinogenic hydrocarbons and estrogens, were applicable to negative results in general:

> "It is evident from the results just described that malignant tumors have not been produced in the monkey by chronic treatment with the female sex hormones and the 3 most commonly used carcinogenic hydrocarbons, methylcholanthrene, benzpyrene and dibenzanthracene. These findings are made more striking by the fact that the carcinogenic compounds have been supplemented in some animals by numerous and extreme inflictions of trauma. Moreover, periodic acute inflammation has been superimposed upon the chronic inflammation that occurs at the sites of application of the carcinogen. This has been especially true when the substance was injected subcutaneously in sesame oil. Negative results are usually considered rather unsatisfactory since their validity is limited in scope. They apply much more rigidly to the experimental conditions than do positive findings. Therefore, a critical analysis of the extent to which the conditions of the present study adhere to the generally accepted requirements for the induction of malignancy is advisable. **Information on all types of experimentally produced tumors indicates that the following factors are of importance: age of host, period of treatment, proper treating agent, method of application, and dosage."** page 106, (4874)

F. SUMMARY STATEMENTS, COUNTER-STATEMENTS AND HIGHLIGHT PUBLICATIONS

The publications explosion during the 1940's is illustrated by citation of over 750 articles that is approximately one-third of the total literature on the subject of pulmonary carcinogenesis. Over 250 articles are quoted above and the remaining 500 are simply referred to by subtopics. However, although articles are briefly mentioned, most are used as secondary citations in articles appearing after 1950 (Part Three), and a few appear after 1966 (Part Four). The publications appearing prior to 1950 will be necessary in the event that a particular form of occupational/environmental or hostal factor will require additional elaboration.

About a score of articles have been selected as highlight publications emphasizing the following conclusions: Prior to 1950, it was not possible to state with absolute certainty that cigarette smoking or any occupational/environmental factor was a significant cause of lung cancer. Several occupational/environmental factors were suspected of causing lung cancer in a susceptible host. Compared to cigarette smoking, the human observations and animal experiments were more extensive in support of the following occupational/environmental factors: fossil fuel products, fuel combustion emissions, and industrial emissions, such as polynuclear aromatic amines,

metalic substances, radioactive substances, and dust particulates. Susceptibility of host to carcinogenic substances were influenced by heredity, diet and nutrition, and tissue reaction to repeated bronchopulmonary irritation. The score of highlight publications support preceding conclusions and supporting details are supplied under Topics A, B, C, D and E.

This concluding Section F consists of a critique of Harris' SOA statements 5.1 to 5.16. The original statements are reproduced below and references used by Harris are numbered using the four-digit citation in the bibliography. Each one of Harris' summary statements is followed by my own counter-statement.

Questionable Increase in Lung Cancer Incidence

> "SOA 5.1. During the period prior to World War I, pathologists, clinicians and vital statisticians began to note an increase in lung cancer - a disease that was relatively obscure prior to 1900. By the late 1920s and 1930s, a dramatic increase in primary lung cancer, predominantly among males, was recognized throughout the United States and Europe. Lung cancer began to overtake cancer of the stomach in clinical and autopsy series and in vital statistics analyses [see Perret (2711); Hoffman (2911) (3131); Arkin and Wagner (3613); Muller 3985); Ochsner and DeBakey 3981) (4164); Menne and Anderson (4156)].

The alleged increase in lung cancer prior to World War I was questionable because of misdiagnosing pulmonary tuberculosis, pulmonary emphysema, parasitic lung disease, and metastatic cancer, for primary lung cancer (see Chapter I). By the late 1920's and 1930's, the increase in primary lung cancer was reported only in cities that has had a thirty year record of autopsies, such as New York, Philadelphia, Boston, Chicago, San

Francisco, Rochester and Detroit. It is wrong to state that the increase in lung cancer incidence "was recognized throughout the United States and Europe" because certification of cause of death was still in its rudimentary stages based on symptomatology with postmortem verification.

> "5.2. At the start, there was controversy concerning the genuineness of the increase in lung cancer incidence. Alternative explanations emphasized improved methods of diagnosis, increased autopsy rates, population aging, changes in disease classification and generally enhanced cancer awareness among physicians. However, such explanations did not accord with other facts, including the increase in the age-specific incidence of lung cancer, the disproportionate rise in lung cancer among males, the rise in lung cancer relative to cancers of other internal organs, and the increased proportion of lung cancers seen at autopsy. Beginning in the late 1920s, a growing number of pathologists, surgeons, vital statisticians, and other scientists realized that, at least since 1920, the rise in lung cancer was genuine, both relatively and absolutely [see Perret (2711); Hoffman (2911) (3131); Mertens (3031); Arkin and Wagner (3613); Muller (3185); Ochsner and DeBakey (3981) (4164); Menne and Anderson (4156); Kennaway and Kennaway (3632) (4759); see also Graham, 1951].

Lung cancer monographers who were also pathologists favored the concept that the increase in lung cancer incidence seen through the 1940's was apparent and unreal. Willis **(4802)**, Fried **(4801)**, Boyd (4130), and Macklin **(4859)** enumerated reasons for misdiagnoses and unreliability of statistics on lung cancer that were applicable prior to, and after 1950.

Cigarette Smoking and Occupational/Environmental Factors

> "5.3 Beginning in the 1920s, a variety of factors were hypothesized as contributing to the striking rise

> in lung cancer. These included: the influenza pandemic of 1918; old tuberculous lesions in lung cancer patients; pre-existing bronchitis and emphysema in lung cancer victims; gasoline fumes containing lead; diesel and gasoline-powered automobile emissions; irritant gases used in World War I warfare; soots, tars and other air pollutants from roads, fuel combustion, and various industrial processes; as well as the rise in cigarette smoking. A concentration of lung cancer cases in the mining district of Schneeberg in Saxony stimulated interest in radioactive substances and certain heavy metals as possible contributors. [See Perret (2711); Hoffman (2911) (3131); Ochsner and DeBakey (4164); Kennaway and Kennaway (3632) (4759)].

Most authorities on lung cancer during the 1940's worked more extensively on non-tobacco causes of lung cancer, than on cigarette smoking. There were human studies and animal experiments supporting the conclusion that lung cancer was caused by the following occupational/environmental factors: fossil fuel products; fuel combustion emissions; soots, tars and air pollutants from roads; industrial emissions; radioactive substances; heavy metals; and polynuclear aromatic hydrocarbons (see above, Topic D).

> "5.4. Beginning in the late 1920s, many surgeons, cancer specialists and other physicians, reporting their clinical experiences with this relatively new cancer, noted that lung cancer patients were almost always heavy cigarette smokers [Table 2]."

Harris selected 21 articles published between 1927 to 1948 to support his statement that "lung cancer patients were almost always heavy cigarette smokers." I have collected more than a hundred additional articles during the three decades prior to 1950, and majority of articles mention cigarette smoke as one of several extrinsic factors in the environment. Approximately a

dozen articles report heavy smoking in their series of lung cancer patients. The remainder of over a hundred articles either quote other investigator's report of heavy smoking or deny that cigarette smoking was a significant causative factor (see Chapter II, page 77; Chapter III pages 204, Chapter IV, page 446).

> "5.5 During the 1930s and early 1940s, the proposition that cigarette smoking caused lung cancer received increasing scientific support (Table 2). Among the several lines of supporting evidence were the following."

For the 1940's, I prepared several tables to illustrate that during this decade, occupational/environmental factors causing lung cancer was receiving increased scientific support. The occupational/environmental human studies and animal experiments exceeded in number the studies that supported the hypothesis that cigarette smoking was a cause of lung cancer (see Topic D, grouping of publications, pages 548 to 561).

<u>Questional Link Between Cancer and Tobacco Use</u>

> "5.6 The concept of cigarette smoking as a cause of lung cancer was consistent with the previously recognized link between pipe or cigar smoking and oral cancer [e.g., Hoffman (3131); Editorial (4117)]."

The link between tobacco use and cancer was explained by direct chemical exposure to cigarette smoke. For oral cancer, link to pipe or cigar smoking was the mechanical irritation of lips (see Supplement, pages 401-410). For lung cancer, cigarette smoking was suspected of causing mucosal irritation, which, together with occupational/environmental factors that also cause

mucosal irritation, lead to lung cancer in a susceptible host.

> "5.7 Further, while pipe and cigar smoking were linked with oral cancer, the widespread inhalation of cigarette smoke, it was reasoned, should be linked mostly to cancer of the lower respiratory tract [e.g., Hoffman (3131); Thys (3540); Ochsner and DeBakey (3981) (4164). Such a hypothesis was supported by observations in cancer patients relating the site of cancer to the type of tobacco used [e.g. Lombard and Doering (2833); Fleckseder (3627); Ahlbom (3765)].

The hypothesis that linked cancer of the lower respiratory tract to type of tobacco used was impossible to prove or disprove because lung cancer patients were also exposed to occupational/ environmental factors, and had undetermined susceptibility associated with heredity, diet and nutrition, and broncho-pulmonary reaction to inhalants. Opinions that strongly linked cigarette smoking to lung cancer were challenged by other investigators who had different interpretations of anti-smoking literature. One anti-smoking physician (Ochsner) reversed his opinion because he could not detect a strong link of heavy smoking in his lung cancer patients.

> "5.8 Moreover, the rise in lung cancer in men parallelled the growth in male cigarette use. The relatively low incidence of lung cancer in women accorded with the delayed emergence of widespread cigarette smoking among females [e.g., Mertens (3031); Lickint (2931); Hoffman (3131); Thys (3540); Arkin and Wagner (3613); Muller (3985); Menne and Anderson (4156); Ochsner and DeBakey (3981) (4164)].

Prior to 1950, most anti-smoking publications emphasized the parallel rise in lung cancer incidence and the prevalence of cigarette use. Some investigators interpreted a lack of increase in lung cancer in women as not supporting a causal hypothesis

(4004) (4079) (4135) 4267) (4554) (4850) (4958). If the hypothesis was correct, incidence in women should have occurred in the 1940's because smoking prevalence had already occurred one or two decades earlier (4772) (4867) (4871).

Animal Experiments on Tobacco Smoke and Coal Tar

> "5.9. In addition, the notion that cigarette smoking caused lung cancer was consistent with the evidence that various tarry products of combustion might be carcinogenic in humans and laboratory animals. Some scientists had produced cancerous lesions in laboratory animals with tobacco smoke and tobacco tars [see Section 4 supra; also Lickint (2931); Muller (3985); Ochsner and DeBakey (4164)]"

Inhalation of tobacco smoke did not induce lung cancer in mice (4914) (4348) and rat (4667). On the other hand, inhalation of coal tar particulate and smoke caused lung cancer in mice. Skin painting with tobacco tar in mice, rats and rabbits, gave conflicting results, whereas squamous cell carcinoma uniformly resulted from skin painting with coal tar and polynuclear aromatic hydrocarbons (4091).

> "5.10 The fact that not all smokers developed lung cancer was consistent with the recognized notion that susceptibility to carcinogens varied among both human populations and experimental strain of animals [e.g., Roffo, as quoted by Grace (4440); American Association of Cancer Research (4348)]."

Susceptibility or sensitivity to lung tumors were demonstrated in selected mice strain receiving polynuclear aromatic hydrocarbons (4086). It should be emphasized that susceptibility or sensitivity was not tested for inhalation of tobacco smoke.

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There was no experimental support that cigarette smoke could alter susceptibility or sensitivity to known carcinogens.

Pre-existing Lung Disease and Air Pollution

> "5.11. What is more, the evidence in support of alternative explanations was much less impressive. Bronchitis, influenza, and tuberculosis were soon rejected. The growth in lung cancer appeared to precede tarring of the roads. Lung cancer incidence had risen in locations where there had been no increase in coal dust, road tarring or automobile traffic. The predominance of lung cancer among men went against the role of generalized air pollution. Comparisons of lung cancer incidence across occupational categories were inconclusive."

The carcinogenic role of bronchitis, influenza and tuberculosis could not be proven or disproved. During the late 1940's, pulmonary tuberculosis, with its fibrogenic reaction, was still suspected as contributing to appearance of cancer in tuberculous patients. The carcinogenic role of coal dust, road tarring or automobile traffic could not be disproved since animal inhalation experiments consistently showed lung cancer. The higher incidence of lung cancer in cities that were thickly populated and heavily polluted with vehicular and industrial emissions, compared to rural areas and less polluted cities, continued to implicate occupational/environmental factors (4862). That most lung cancer patients in heavily polluted areas were also smokers was raised after 1950 and is described in Part Three.

> "5.12. Finally, although coal dust, radioactive isotopes, chromates, nickel and arsenic compounds and silica remained suspect, exposures to such agents did not appear sufficient to account for the large, dramatic

> increase in lung cancer. As in the earlier experience with oral cancer, researchers recognized that tobacco need not be the only causative factor. [See citations in Ochsner and DeBakey (4164); Menne and Anderson (4156); also Kennaway and Kennaway (4709)]

Any one occupational/environmental factor "need not be the only causative factor." For example, a Schneeberg miner was exposed, not only to radioactive isotope but also to arsenic, silica and cadmium in work environment. He was also exposed to ambient air pollutants such as coal dust, road tar, vehicular emissions and industrial emissions. The same miner might have been a smoker who was ingesting food carcinogens, and had inherited susceptibility to lung cancer. The multiple extrinsic and intrinsic factors influencing susceptibility to lung cancer apply to non-miners, housewives, and outdoor workers listed in a Table of Case Reports (see above, pages 447 to 454).

> "5.13. By the late 1930's, cigarette smoking histories were being intentionally taken among lung cancer patients at major hospitals and centers [see Levin, Goldstein and Gerhardt, 1950; Sadowsky, Gilliam and Cornfield , 1953]."

There was no evidence that by the late 1930's, "cigarette smoking histories were being intentionally taken among lung cancer patients at major cancer hospitals and centers." I have examined publications from cancer hospitals and centers and found that routine questioning of smoking habits occurred only in one Veteran's Hospital. Even publications by clinicians aware of antismoking literature did not report on the smoking habits of

their own series of patients with lung cancer (4046) (4718) (4866).

Control Study From Nazi Germany

> "5.14. By 1939, a carefully age-matched comparison of lung cancer patients with non-cancer patients confirmed a significant excess of heavy smokers in the cancer group and a marked excess of nonsmokers in the control group [Muller (3985)]."

Muller's article appeared just before World War II, when most researchers were highly suspicious of publications written by Nazi physicians. The 1939 article was a summary of Muller's thesis for his doctorate degree. There were no subsequent publications by Muller listed in available literature indices.

> "5.15. During the 1940s, three additional clinical studies comparing lung cancer patients and control subjects [Schairer and Schoniger (4311); Potter and Tully (4560); Wassink (4893) confirmed the previously reported excess of heavy smokers among lung cancer cases (Table 2)]."

Schairer & Schoniger published their article during World War II under the following affiliation: Scientific Institute for Research on the Dangers of Tobacco in Jena, presently in East Germany (4311). There has been no subsequent publication by both authors and one author is listed in a current directory of German physicians. Wassink's publication (4893) related to Dutch patients, who, like German patients, have different prevalence of smoking habits compared to Americans. The claim of Potter & Tully (4560) that there was an excess of heavy smokers among lung cancer cases referred to all forms of tobacco use, mostly pipe

and cigars, and less of cigarette smokers (see Supplement, page 397).

Non-tobacco Factors Causing Lung Cancer

> "5.16. Thus, by late 1930s and early 1940s, a substantial number of researchers had already pointed to cigarette smoking as the main cause of lung cancer (Table 2). Although definitive, unimpeachable evidence was not yet available,the cigarette smoking-lung cancer connection was a sufficiently real possibility to merit serious concern. The notion that cigarette smoking caused lung cancer was well reasoned, clearly articulated, and repeatedly asserted."

The above statements on cigarette smoking equally apply to role of environmental/occupational factors and hostal factors influencing susceptibility. There were more authors who conducted research and published articles, review and monographs on non-tobacco factors causing lung cancer. Quotations from lung monographers conclude this Chapter:

"Neither occupation nor smoking habits seemed of any special significance in this particular series." - Ochsner, DeBakey & Dixon (4773);

"It is quite possible that inhalation of cigarette smoke is an important factor, but proof of this will entail much more pathological and experimental research." - Willis (4802);

"Evidence thus far adduced is contrary to the idea that bronchogenic cancer is caused by tobacco." - Fried (4801).

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